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ARCHIVES OF PATHOLOGY

VOLUME 15 MARCH, 1933 NUMBER 3

HISTOLOGIC CHANGES IN THE THYROID GLAND OF THE RABBIT FOLLOWING INJECTION OF URINE

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WICHITA, KAN.

Krjlow and Sternberg [1] recently reported the occurrence of structural changes in the thyroid gland of the female rabbit following copulation. As early as eleven hours after coitus, the thyroid gland showed marked enlargement and hyperemia. Histologically, the colloid had almost completely disappeared, and the height of the epithelial cells lining the acini had much increased.

Friedman [2] recommended for the biologic pregnancy test that, in place of mice, rabbits be used, as in these ovulation is provoked by the urine of pregnant women in the same manner as it is provoked physiologically only after copulation.

In the light of these findings, the question presented itself, whether in rabbits with a positive Aschheim-Zondek reaction, the thyroid gland would show changes similar to those following copulation. If this were the case, it was hoped that an additional sign of a positive pregnancy test might be found by examining the thyroid gland of the rabbit following the injection of urine.

The following study is based on a microscopic examination of the thyroid glands of seventy-three female rabbits. Sixty-four glands were obtained from animals used for the biologic pregnancy test. Tests were performed during every month of the years 1931 and 1932, a measure which excluded variations in the structure of the thyroid gland due to seasonal changes. All animals were isolated for several weeks previous to the Aschheim-Zondek test and were fed only with alfalfa-hay and rolled oats, to avoid any possible histologic changes caused by unbalanced food. The cages were kept scrupulously clean, since McCarrison stressed uncleanliness as one important factor in producing hyperplasia of the thyroid gland.

In this laboratory, the following technic of the Aschheim-Zondek test is used as a routine. The slightly acid, filtered morning urine is injected intramuscularly into a female rabbit, 3 months old; 8 cc. is

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Aided by a grant from the Committee on Scientific Research of the American Medical Association.

1. Krjlow, L. N., and Sternberg, A. J.: Endokrinologie **10**:37, 1932.
2. Friedman, M. A.: Am. J. Physiol. **90**:617, 1929.

given on the first day and the same amount on the second. The rabbit is killed with chloroform forty-eight hours after the first injection and studied at autopsy. The test is regarded as indicative of pregnancy when at least one corpus hemorrhagicum or one corpus luteum is found with the unaided eye in one ovary. Microscopic examination of the sex organs is made in every case. For this study of the effects of

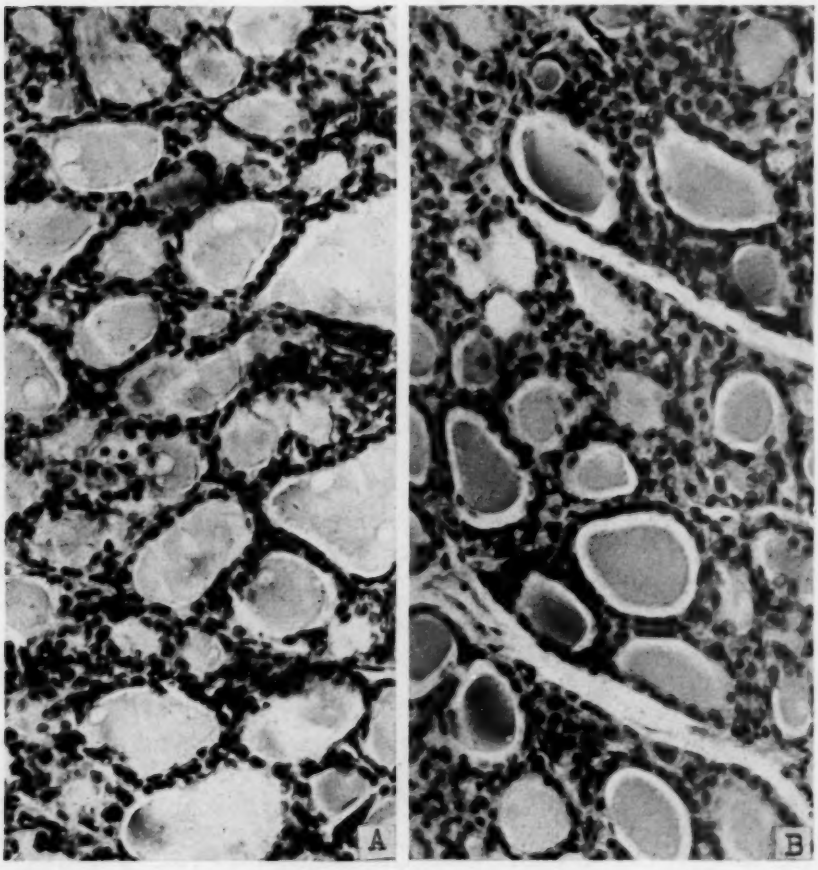

Fig. 1.—Normal thyroid glands of 3 months old female rabbits: *A*, during summer; *B*, during winter.

injected urine on the thyroid gland, the cervical organs, including the trachea, esophagus and thyroid gland, of sixty-four test animals were removed immediately after death and placed in 10 per cent formaldehyde. Numerous paraffin sections were made in horizontal planes, and the sections that included the isthmus and both lobes of the thyroid gland were selected for the microscopic description.

In figure 1 *A* and *B* are shown normal thyroid glands of 3 months old female rabbits into which urine had not been injected, but which otherwise had been kept under the same conditions as the test animals. The normal thyroid gland of the young female rabbit is composed of round or oval acini, well filled with dense colloid. The acinar epithelium is low, having an average height of 4 microns. The diameter of most

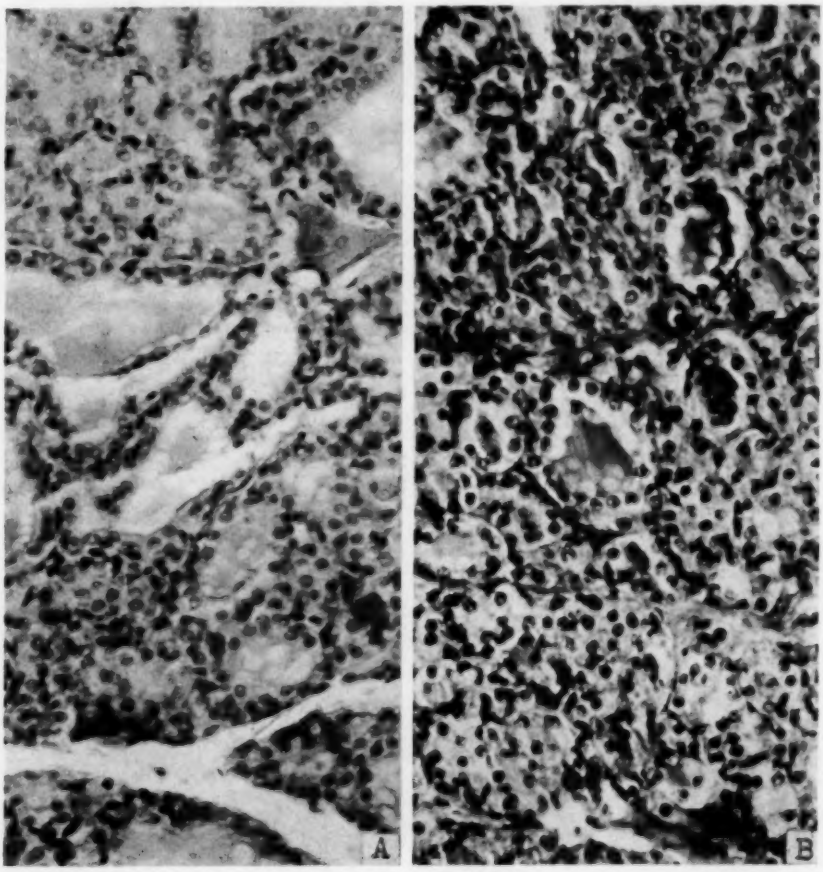

Fig. 2.—*A*, slight hyperplasia of the thyroid gland of a rabbit following injection of urine from a pregnant woman; *B*, marked hyperplasia of the thyroid gland of a rabbit following injection of urine from a pregnant woman. Both rabbits showed a positive Aschheim-Zondek reaction in the ovaries.

acini varies between 80 and 120 microns. Dense cellular areas, with very narrow lumens, are almost completely absent during the summer months, and only scantily present, in the center of the gland, during the winter. The colloid is well stained with eosin and as a rule fills the whole lumen. Vacuoles in the periphery of the colloid disk, indicating

a thinner consistency, are exceptional. The capillaries surrounding the acini are poorly filled with red blood cells. These findings were uniform in all the control animals.

In figures 2 and 3 are shown thyroid glands of rabbits which were used in the Aschheim-Zondek test. The great majority of these glands differed widely in structure from the normal controls. In fifty-

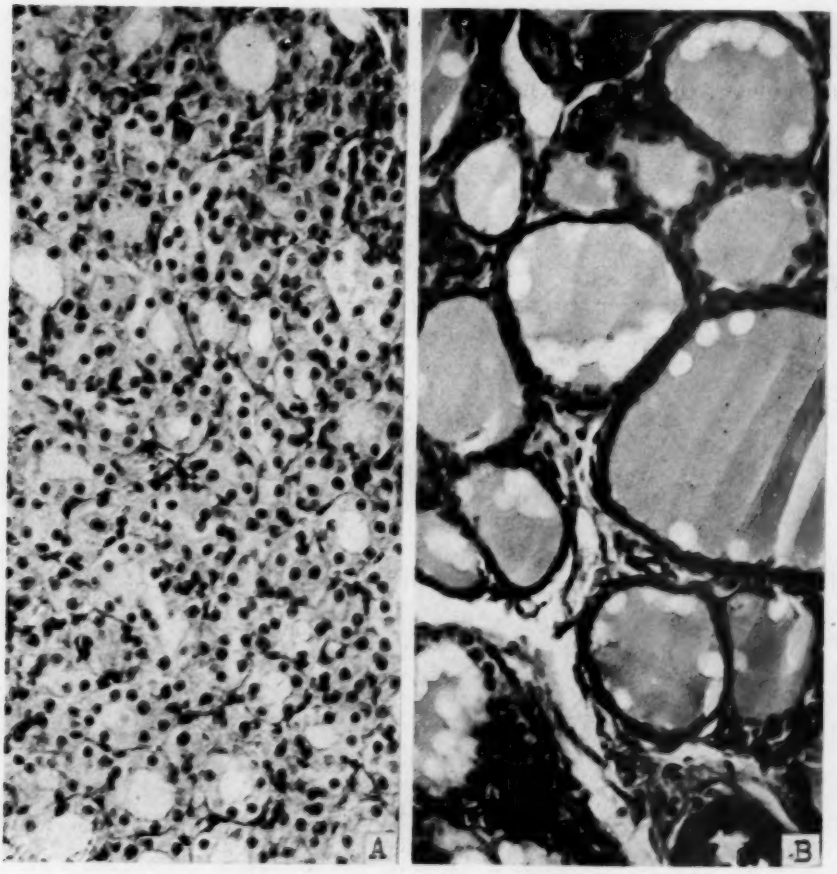

Fig. 3.—*A*, marked hyperplasia of the thyroid gland in a rabbit following injection of urine from a nonpregnant woman; *B*, absence of reaction of the thyroid gland after injection of urine. Eight of the sixty-four rabbits used for the pregnancy test did not show any hyperplastic changes in the thyroid gland.

six of the sixty-four glands from test animals, hyperemia of the entire gland was evident even to the unaided eye. The colloid was stained much more lightly, often appeared to be finely granular and, in many acini, had disappeared. In most follicles, only a small portion of the lumen was filled, and large, unstained vacuoles had formed on the

periphery. The epithelial cells of the acini were high cuboid or columnar, measuring from 8 to 12 microns; their cytoplasm was stained light blue. In the larger follicles, infoldings of the wall and true papillations were frequent (fig. 2*A*). The glands of twenty-one test animals looked almost completely solid owing to very small acini, of round or tubular form and without eosin-stained colloid (fig. 2*B*).

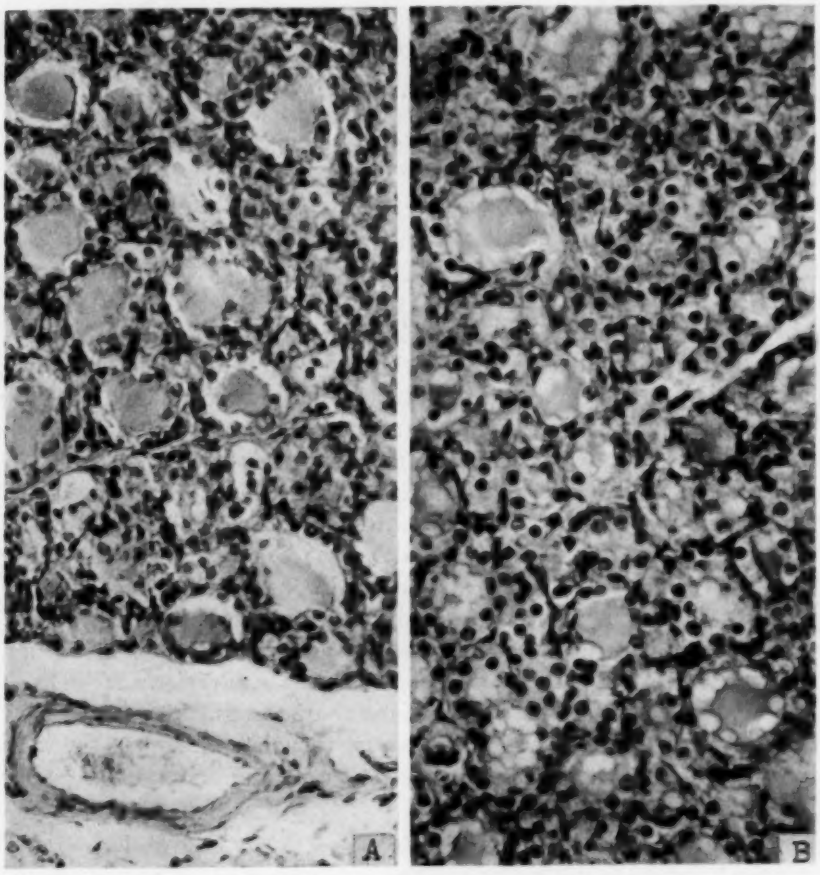

Fig. 4.—*A*, changes in the thyroid gland after injection of urine from a nonpregnant woman together with 4 mg. of potassium iodide; *B*, hyperplasia of the thyroid gland in a young female rabbit following implantation of the anterior lobe of the hypophysis.

Only eight of the sixty-four test animals presented pictures without definite changes except perhaps the presence of more vacuoles on the margin of the colloid pearls and very slightly increased height of the epithelial wall. These eight thyroid glands have been listed as negative in reaction (fig. 3*B*).

The hyperplastic changes observed in the large majority of animals after the injection of urine did not differ according to the outcome of the pregnancy test. Of twenty-six animals with a positive Aschheim-Zondek reaction of the ovaries, eighteen showed a moderate, and eight a marked, hyperplasia of the thyroid gland, while, of thirty rabbits giving a negative reaction, seventeen presented moderate and thirteen marked changes. The eight thyroid glands showing a very slight reaction or none represented three negative and five positive Aschheim-Zondek tests. That the changes in the thyroid gland were without relation to the reaction of the ovaries was illustrated plainly in the following case: Urine from a woman was injected a few days after the first missed menstrual period, and a negative Aschheim-Zondek reaction was obtained. A few weeks later, from the same woman, urine was again injected into a rabbit of the same breed and age, and this time the ovaries showed many corpora hemorrhagica. Not only in the second, but also in the first, instance, the thyroid gland of the rabbit showed marked hyperplasia. The urine from a boy, 10 years old, apparently without endocrine disorders, produced marked hyperplasia of the thyroid gland, while the ovaries of the rabbit receiving the injection showed only dilated follicles with clear content. It was thought that the negative findings in eight thyroid glands—in five positive and three negative Aschheim-Zondek tests—might be explained by a higher content of iodine in the urine, preventing hyperplasia of the thyroid gland. I injected, therefore, in four instances, 4 mg. of potassium iodide together with urine. This dose of iodine is much larger than could be expected under normal conditions in the urine. But the glands of these animals were far from normal; they had much smaller acini—on the average, 40 microns in diameter—and the epithelium measured 6 microns in height. The only striking difference in these four thyroid glands was in the consistency of the colloid. It was very dense, stained deep red and was without vacuoles, filling out the acini completely. The capillaries of the interacinar septums were poorly filled (fig. 4 *A*).

COMMENT

In the available literature, I could not find any report which mentions thyroid gland changes in rabbits used for the biologic pregnancy test. This is surprising, since the frequently performed Aschheim-Zondek test presents such easily accessible material. When Chesney, Clawson and Webster [3] reported the production of goiters in rabbits by feeding cabbage, it was emphasized by Marine [4] that this method

3. Chesney, A. M.; Clawson, T. A., and Webster, B.: Bull. Johns Hopkins Hosp. **43**:261, 1928.

4. Marine, D.: Ann. Int. Med. **4**:423, 1930.

constitutes an easy and certain experimental means for studying hyperplasia of the thyroid gland. From McCarrison's [5] and Zeckwer's [6] experiments it is obvious that there exist marked seasonal variations and also an individual susceptibility of certain breeds of rabbits which make the production of goiter by cabbage not absolutely dependable. The injection of urine, on the other hand, was effective in producing typical histologic changes in 87.5 per cent and as early as forty-eight hours after the first injection. The microscopic changes observed two days after the injection of urine were apparently as marked as those found after several months' feeding of cabbage, if one may judge by comparison of figures *2 B* and *3 A* in this paper with figure 6 of the original paper by Chesney and his co-workers.[3] Since my observations were uniform for every month of two years, and since no variations occurred in the different breeds of rabbits (obtained from local dealers), I feel certain that the injection of urine presents an almost sure and very easy means for producing hyperplasia of the thyroid gland.

Loeb [7] studied the effect of injection of urine from pregnant women on the thyroid gland in the immature guinea-pig. He examined microscopically the sex organs and thyroid glands of forty-one guinea-pigs into which had been injected daily amounts of urine from pregnant women varying between 1 and 4 cc., over periods from one to twenty-one days. Loeb arrived at the conclusion that urine of pregnant women is entirely inert in its effect on the thyroid gland. His results contradict those of Aron,[8] who found that on injection of normal urine the thyroid gland of the young guinea-pig undergoes a characteristic reaction, consisting in a 40 per cent increase in weight and in histologic evidence of hyperactivity of slight degree, confined to the center of the gland. The acinar epithelium appeared higher than normal, and vacuoles had formed in the colloid as the result of resorptive processes. The same author mentioned briefly that the thyroid gland of the rabbit reacts also with mild hyperplasia toward injection of urine. Aron made the further remark that urine from pregnant women is not more active in its thyrotropic influence than urine from nonpregnant women or from males. My observations on rabbits are in accord with Aron's view, except that in my animals the changes were evidently of a much higher degree.

In regard to the nature of this active substance in the urine, producing the characteristic hyperplasia of the thyroid gland, Aron's contention seems to be very plausible, that it is a hormone of the anterior lobe of the hypophysis which is excreted in the urine. Loeb

5. McCarrison, R.: Indian J. M. Research **18**:1311, 1931.
6. Zeckwer, I. T.: Am. J. Path. **8**:235, 1932.
7. Loeb, L.: Endocrinology **16**:129, 1932.
8. Aron, M.: Compt. rend. Soc. de biol. **105**:585, 1930.

and Basset [9] first called attention to a thyrotropic hormone secreted by the anterior lobe of the pituitary gland. By injection of acid or alkaline extract of the anterior lobe of the hypophysis into the guinea-pig, these authors were able to produce marked hyperplasia of the thyroid gland. The histologic changes which I obtained in the thyroid gland of a young female rabbit forty-eight hours after implantation of the anterior lobe of the hypophysis of the beef are evident from figure 4 *B*. Aron [8] extended the experiments of Loeb and Basset [9] to rabbits, cats and dogs and obtained the same positive results. Simultaneous injection of pituitary extract and potassium iodide produces, according to experiments of Silberberg,[10] a typical hyperplasia in some areas of the gland, while in other portions histologic changes typical for the iodine effect are found. His description is in accordance with my observation after injection of urine together with 4 mg. of potassium iodide (fig. 4 *A*).

Since definite chemical or physical properties of this thyrotropic hormone of the hypophysis are not yet known, it is not certain that the active substance in the urine which acts on the thyroid gland is identical with the hormone secreted by the anterior lobe of the pituitary gland. Further study is required to establish their identity before Aron's view can be accepted, that histologic examination of the thyroid gland after injection of urine may serve as a biologic test for secretory disturbances of the hypophysis. In my eight cases in which injection of urine had no influence on the thyroid gland of the rabbit, I was unable to diagnose clinically any functional deficiency of the pituitary gland.

At this time it can be said only that the thyrotropic agent of the urine must be entirely different from the substance which acts on the ovaries (prolan). The reaction of the thyroid gland was, in my cases, clearly independent of the result of the Aschheim-Zondek test, since the hyperplasia of the gland was found after injecting urine from pregnant and nonpregnant women and even from males. My observations support the view held by Janssen and Loeser,[11] that prolan, obtained by Zondek's method from the urine of pregnant women, is entirely inert in its effect on the thyroid glands of animals.

SUMMARY

Of sixty-four rabbits used for the biologic pregnancy test, fifty-six (87.5 per cent) showed characteristic changes in the thyroid gland, consisting of hyperemia, liquefaction of colloid and hyperplasia of the acinar

9. Loeb, L., and Basset, R. B.: Proc. Soc. Exper. Biol. & Med. **27**:490, 1930.
10. Silberberg, M.: Proc. Soc. Exper. Biol. & Med. **27**:166, 1929.
11. Janssen, S., and Loeser, A.: Arch. f. exper. Path. & Pharmakol. **163**:517, 1931.

epithelium. The reaction was definite forty-eight hours after the first intramuscular injection of urine. These hyperplastic changes were moderate in thirty-five and marked in twenty-one animals. Hyperplasia of the thyroid gland occurred in rabbits irrespective of the results of the Aschheim-Zondek test.

The assumption seems justified that the active substance in the urine is identical with the thyrotropic hormone of the anterior lobe of the pituitary gland. It is no doubt different from the active substance present in the urine of pregnant women which acts on the ovaries.

Injection of urine into rabbits presents an easy, rapid and almost certain method for studying the histogenesis of hyperplasia of the thyroid gland.

COCCIDIOSIS OF THE LIVER IN RABBITS

II. EXPERIMENTAL STUDY ON THE MODE OF INFECTION OF THE LIVER BY SPOROZOITES OF EIMERIA STIEDAE

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NEW YORK

The mode of infection of the biliary tract by the sporozoites of Eimeria stiedae is not known. Since the sporozoites are liberated from the oocysts by the action of the pancreatic juice,[1] presumably below the entrance of the pancreatic duct into the duodenum, the question arises as to how the sporozoites reach the epithelial cells of the intrahepatic bile ducts. Three theories have been advanced to answer this question:

1. The sporozoites, by their active movements, swim up within the lumen of the duodenum until they reach the common bile duct, and then through the common bile duct into the intrahepatic bile ducts, where they finally lodge.

It has been suggested [2] that the sporozoites wander upstream inside the duodenum until they reach the orifice of the common bile duct, penetrate the epithelial cells of its distal portion, and start their schizogony cycle; the schizonts or the merozoites then infect the epithelial cells of the bile duct in the proximal direction until they finally reach the intrahepatic bile ducts.

2. The sporozoites penetrate the wall of the duodenum and are then carried by the radicals of the portal vein into the liver.

3. The sporozoites reach the liver by way of the lymphatics from the mucosa of the intestine.

The methods I applied in attacking this interesting problem were as follows:

1. Histologic study of the earliest lesions of the liver after infection by mouth.

2. Ligation of the extrahepatic bile duct leading to one lobe of the liver, followed by infection of the animal by mouth. In this experiment, the sporozoites were prevented from entering one of the lobes of the liver by way of the bile duct, while their entrance to the same lobe through the blood stream was not obstructed.

From the Department of Pathology, College of Physicians and Surgeons, Columbia University.

1. Smetana: Coccidiosis of the Liver in Rabbits: 1. Experimental Study on the Excystation of Oocysts of Eimeria Stiedae, Arch. Path. **15**:175, 1933.

2. Seifried: Ergebn. d. allg. Path. u. path. Anat. **22**:513, 1927.

3. Injection of liberated sporozoites into a mesenteric vein.

4. Anatomic study of the lymphatic connections between the intestines and the liver.

STUDY 1

The details of the histologic study of coccidiosis will be taken up in a subsequent paper, "The Histogenesis of Coccidiosis of the Liver." Here I shall state merely that the earliest lesions of coccidiosis of the liver appear about seven days after the infection and are found first in the small-sized and medium-sized intrahepatic bile ducts; the distal portion of the common bile duct and the extrahepatic bile ducts do not show lesions at that time, but become secondarily infected later by merozoites liberated from infected epithelial cells of the intrahepatic bile ducts. These findings exclude the possibility of a primary infection of the distal end of the common bile duct and the spreading of the infection "by contact" up the bile ducts into the liver.

STUDY 2

The possibility that the sporozoites travel up the lumen to infect the intrahepatic bile ducts still remains, but the following experiments convincingly exclude that.

Technic.—Under ether anesthesia the extrahepatic bile duct leading to the right lobe of the liver was tied by a ligature. I chose this lobe of the liver because in most rabbits this lobe is practically separated from the rest of the liver, and its bile duct branches off almost rectangularly from the main bile duct, making it easier to bind it successfully without injury to the main duct. In tying off this duct, one must be careful not to bind a small artery that runs parallel to the duct, as necrosis of the right lobe of the liver might occur. Likewise, injury to the portal vein should be carefully avoided.

After successful ligation of the branch of the common bile duct, the gallbladder was punctured, and most of the bile present was aspirated through a syringe. This operation was performed in order to examine the bile for oocysts. The procedure was as follows: A loose noose of surgical silk was placed around the fundus of the gallbladder; the wall of the fundus of the gallbladder was then perforated, the bile aspirated into the syringe and, with the needle still in the gallbladder, the wall of the fundus was tied to the needle by closing the noose. After removal of the needle, the puncture was completely closed by tightening the noose. This operation is harmless and can be repeated if necessary. Hemorrhage, which rarely occurs, resulted in one instance in the formation of a gallstone, which in turn obliterated the lumen of the gallbladder.

The examination of the gallbladder is of the utmost importance, as oocysts present in this bile indicate that the animal has or has had coccidiosis of the liver. Although the actual length of time of their presence in the bile of the gallbladder has not been determined, they can often be found when the liver no longer shows evidence of coccidiosis. The fact that oocysts are found in the bile of the gallbladder in

cases of coccidiosis of the liver was first described by Pérard,[3] who used this method for determining the presence of coccidiosis of animals at autopsy. For the present study, however, it seemed imperative to know whether or not the animals were free from coccidiosis before the operation, because otherwise the results of the experiment would seem rather doubtful. Examination of the bile of the gallbladder proved to be the most reliable of all methods to determine the presence of an infection, much more so than biopsy of hepatic tissue or examination of the feces of the animals. In many cases in which oocysts were found in the gallbladder, no evidence of coccidiosis could be found in sections of hepatic tissue obtained for biopsy. Sometimes small, isolated lesions were hidden somewhere and could not be seen at operation without injury to the liver. Likewise examinations of feces sometimes failed to disclose oocysts of Eimeria stiedae, though oocysts were present in the gallbladder and encapsulated lesions could be found in the liver at autopsy. The absence of oocysts in the bile of the gallbladder is, however, not an absolute proof of the absence of coccidiosis of the liver, since during the stage of schizogony no oocysts are formed. In order to detect this early stage, biopsy of hepatic tissue is sometimes helpful, but unless the infection is diffuse, a negative outcome of the biopsy is not absolutely conclusive. By selecting young, healthy rabbits of good stock, approximately 4 weeks of age, one can be reasonably sure of using animals free from coccidial infestation of the liver. Younger animals are too frail to stand the operation, and those that have reached the age of 8 weeks are rather apt to have developed coccidiosis.

One or two days after the ligation of the duct the animals were infected with from 5 to 10 cc. of a saline suspension of sporulated oocysts of Eimeria stiedae by stomach tube and were kept in separate cages for varying lengths of time; some died spontaneously and others were put to death. In some cases, at autopsy, india ink was injected into the common bile duct in order to prove that successful ligation of the duct leading to the right lobe of the liver had taken place. In all cases, the bile duct of the right lobe was dissected free from the adhesions resulting from the operation, and the damage to the lobe, after tying off the duct, and the ligature were inspected. The right lobe of every animal used successfully for these experiments showed varying stages of cirrhosis externally. On cut sections, the bile ducts were found greatly enlarged, containing a thick, colorless fluid similar to that found in hydrops of the gallbladder. At autopsy, the bile of the gallbladder was reexamined for cocysts.

The results of nine experiments of this kind are given in table 1.

Two of the nine experiments are not considered valid, because of the presence of oocysts in the bile of the gallbladder before ligation of the bile duct (animals 1 and 2). In one experiment (animal 9) the bile

3. Pérard: Compt. rend. Acad. d. sc. **178**:2131, 1924; **179**:1436, 1924; Ann. Inst. Pasteur **38**:953, 1924; **39**:505, 1925.

duct of the right lobe was found at autopsy to have been incompletely ligated, since india ink passed through it into the right lobe after injection of the dye into the common bile duct. The lesions in the liver of animal 6 seemed older than one would expect twenty-two days after infection, and the result of this experiment is consequently doubtful. In one case (animal 5), no evidence of coccidiosis was found in any of the lobes, probably because of the shortness of the time after infection.

TABLE 1.—*Ligation of Extrahepatic Bile Duct of Right Lobe of Liver; Infection with Oocysts (Eimeria Stiedae) by Stomach Tube*

Animal	Age, Wk.	Oocysts in Bile of Gall-bladder Before Exper.	Material Used for Infection	Duration of Experiment, Days	Oocysts in Bile of Gall-bladder at Autopsy	Findings at Autopsy, Liver	Result
1	10	+	LC*	11	+	Old foci and early schizogony; reinfection; cirrhosis of right lobe	Invalid
2	10	+	LC*	6	+	Old foci; necrosis of right lobe (artery ligated)	Invalid
3	4	0	LC*	13	+	Coccidiosis of all lobes; schizogony and early gametogony; early biliary cirrhosis of right lobe	+
4	4	0	LC*	11	+	Coccidiosis of all lobes; schizogony, advanced; gametogony; early biliary cirrhosis of right lobe	+
5	5	0	LC*	6	0	No evidence of coccidiosis.....	0
6	5	0	LC*	22	+	Healing coccidiosis of all lobes; partial necrosis of right lobe (branch of artery tied)	?
7	4	0	LCF†	27	+	Coccidiosis of all lobes; schizogony and gametogony; cirrhosis of right lobe	+
8	4	0	LCF†	15	+	Coccidiosis of all lobes; schizogony and gametogony; early biliary cirrhosis of right lobe	+
9	4	0	LCF†	14	+	Coccidiosis of all lobes; schizogony and gametogony; bile duct of right lobe not ligated	Invalid

* Oocysts of Eimeria stiedae collected from lesions of the liver.
† Oocysts of Emieria stiedae collected from the feces.

In every other case, all lobes of the liver showed coccidiosis of the bile ducts of stages corresponding to the lengths of time of infection.

From the positive outcome of these experiments, it would seem that the sporozoites do not enter the liver by way of the bile ducts; it can at least be said that ligation of the duct leading to one of the lobes does not prevent the sporozoites from entering this lobe.

STUDY 3

Since the successful infection of the right lobe of the liver after ligation of its bile duct suggested that the sporozoites might not enter

the liver by way of the bile duct, attempts were made to find out whether liberated sporozoites injected into a mesenteric vein would cause coccidiosis of the intrahepatic bile ducts. These experiments were carried out in the following manner:

Technic.—Young, healthy rabbits of good stock were chosen and kept in separate cages for several days prior to the experiment. During this time their feces were examined daily for oocysts of Eimeria stiedae, and animals showing such oocysts were excluded from the experiment.

On the day of the experiment, 10 drops of oocysts were placed in 5 cc. of either pancreatic juice of a dog or natural intestinal juice of a rabbit or an aqueous solution of steapsin of p_H 7.5 and put in the incubator at 37 C. From four to six hours after these oocysts had been exposed to the tryptic action of the mediums, smears were made, and the percentages of excystation were determined. Likewise; free, moving sporozoites were counted. The samples were then centrifugated, washed twice with sterile saline solution, and finally suspended in 5 cc. saline solution.

The rabbits were then etherized, and after laparotomy the gallbladder was punctured and the bile aspirated; in addition, a piece of liver was excised. After this had been accomplished, a fairly large mesenteric vein was selected, and into it from 2 to 5 cc. of the saline solution containing the oocysts, previously treated with the tryptic mediums, was injected. If considerable bleeding occurred after withdrawal of the needle, the blood vessel was ligated. The laparotomy wound was closed in the usual manner. The animals thereafter were kept in separate cages for from nine to forty-nine days. Of ten animals used for this experiment, two died spontaneously (table 2, animals 3 and 6); the others were put to death. At autopsy, the gallbladder was punctured and its bile reexamined for oocysts. The liver was fixed in Zenker's solution, and several sections were subsequently examined microscopically. Two normal animals were kept under the same conditions in order to see whether they would develop coccidiosis spontaneously. In order to limit the errors due to a possible spontaneous infection, most of the animals were killed from nine to fourteen days after the experiment.

The results of ten such experiments are given in table 2.

Three of the animals (table 2, animals 3, 4 and 6) showed the presence of oocysts in the bile of the gallbladder at the time of operation, and the experiments on these are considered not valid. One animal (2) remained free from oocysts. The result of another experiment (animal 5) is doubtful because oocysts were found in the bile of the gallbladder nine days after the injection of liberated sporozoites into the mesenteric vein; this is too soon after injection; the animal probably had an early spontaneous infection to begin with. Four animals (7, 8, 9 and 10) showed advanced schizogony in some parts of the liver, corresponding in stage to the length of time elapsed after the operation. Healing lesions were found in the liver of animal 1, which lived for forty-eight days after operation. The two controls showed no evidence of coccidiosis of the liver.

Unfortunately, the method of injecting oocysts which had been exposed to the tryptic action of certain mediums was defective, because

TABLE 2.—*Injection of Liberated Sporozoites of Eimeria Stiedae into Mesenteric Vein*

Animal	Age, Weeks	Oocysts in Bile of Gallbladder Before Experiment	Biopsy of Liver	Material Used for Injection			Duration of Experiment, Days	Oocysts in Bile of Gallbladder at Autopsy	Findings at Autopsy, Liver	Result
				Medium	Type of Oocysts	Excystation, per Cent				
1	26	0	No evidence of coccidiosis	Intestinal juice, rabbit	LC*	30	48	+	Healing coccidiosis.....	+
2	4	0	No evidence of coccidiosis	Intestinal juice, rabbit	LC*	36	29	No bile gallstone	No evidence of coccidiosis.....	0
3	4	+	No evidence of coccidiosis	Steapsin, 5%	LC*	20	2	+	Chronic coccidiosis.....	Invalid
4	4	+	Coccidiosis ?	Steapsin, 5%	LCF†	15	9	+	Healing coccidiosis.....	Invalid
5	4	0	No evidence of coccidiosis	Steapsin, 5%	LCF†	39	9	+	Early coccidiosis, schizogony	?
6	5	+	No evidence of coccidiosis	Pancreatic juice, dog	LCF†	30	23	+	Chronic coccidiosis.....	Invalid
7	4	0	No evidence of coccidiosis	Pancreatic juice, dog	LCF†	18	12	0	Early coccidiosis, schizogony	+
8	4	0	No evidence of coccidiosis	Pancreatic juice, dog	LCF†	30	10	0	Early coccidiosis, schizogony	+
9	4	0	No evidence of coccidiosis	Pancreatic juice, dog	LCF†	30	13	0	Early coccidiosis; schizogony, advanced; early gametogony	+
10	4	0	No evidence of coccidiosis	Pancreatic juice, dog	LCF†	30	14	0	Early coccidiosis; schizogony, advanced; early gametogony	+
11	4	0	No evidence of coccidiosis	(No injection)	.....	..	10	0	No evidence of coccidiosis.....	Control
12	4	0	No evidence of coccidiosis	(No injection)	.....	..	12	0	No evidence of coccidiosis.....	Control

* Oocysts of Eimeria stiedae collected from lesions of the liver.

† Oocysts of Eimeria stiedae collected from the feces.

the liberated sporozoites could not be separated from the empty shells or from oocysts showing no evidence of excystation; in addition, a certain amount of débris was always present. Therefore, injections of this material into the mesenteric vein carried oocysts and débris, as well as free sporozoites, into the liver, causing a severe foreign body reaction in the tissues of the portal fields. Besides, many of the liberated sporozoites probably were badly damaged by the manipulation in removing the tryptic medium, the washing, etc., so that the survivors, able to start the infection of the bile ducts, were few. These factors can be held responsible for the limited lesions found at autopsy in the livers of these rabbits. Nevertheless, it seems safe to conclude from the results of these experiments that liberated sporozoites injected into a mesenteric vein can cause coccidiosis of the intrahepatic bile ducts.

STUDY 4

The question whether the sporozoites travel to the liver by way of the lymphatics was difficult to answer in a direct way. The method of injection of liberated sporozoites into lymphatics of the intestinal wall could not be applied, because of the coarseness of the material, which would block the lymphatics. Therefore I chose to investigate the lymphatic connections between the wall of the small intestine and those of the liver and bile ducts.

Technic.—Under ether anesthesia, laparotomy was performed on three rabbits, and 1 cc. of india ink was injected into the lymphatics of the wall of the duodenum. Almost immediately the dye spread, not only around the duodenum, but in the mesentery, where lymphatics were visible running parallel to blood vessels. After the successful injection, a piece of liver was excised in order to prove that the india ink had not been injected into a blood vessel, which would carry the particles immediately into the liver. The animals were then put to death one, two and ten days after the operation, and the lymphatics were inspected grossly and microscopically. The animal that was killed two days after the injection showed india ink granules in the Kupffer cells of the liver, in sections of the tissue obtained by biopsy and at autopsy, showing that some of the dye had accidentally reached a small blood vessel.

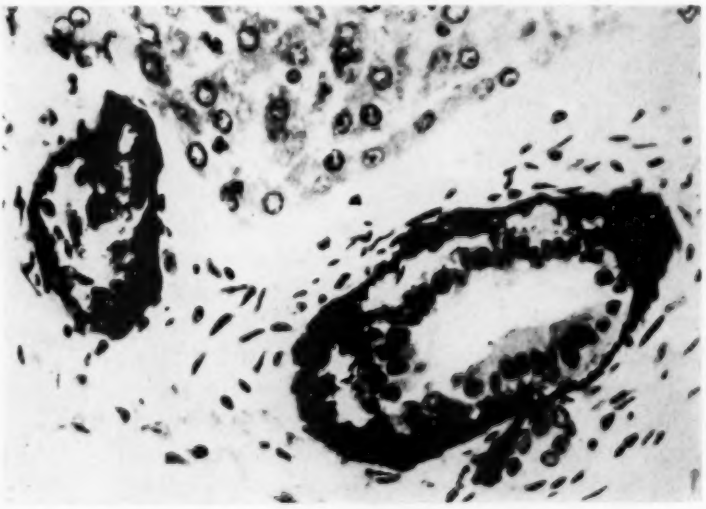
No trace of the india ink could be detected in any part of the liver of the rabbits killed one and ten days after the injection of the ink into the lymphatics of the intestinal wall, while the mesenteric lymph nodes were heavily stained. None of the sections taken from the portal vein and extrahepatic bile ducts showed india ink in the adjacent lymphatics.

The presence of lymphatics around bile ducts and branches of the portal vein, however, can easily be demonstrated by injecting india ink, post mortem, into the wall of the common bile duct or that of the portal vein at the porta hepatis. After successful injection, lymphatics can be seen in sections around these structures in many of the portal fields (fig.).

This informative study seemed sufficient to rule out the lymphatics as the portal of entry of sporozoites from the intestines into the liver. Owing to the mesenteric lymph nodes acting as filters, the sporozoites would be prevented from reaching the liver even if lymphatic connections between it and the intestines existed.

SUMMARY AND COMMENT

In order to appreciate the problem of the mode of the infection of the bile ducts of the liver by sporozoites, it has to be pointed out that in the rabbit the pancreatic duct empties into the duodenum about 40 cm. (15 inches) below the common bile duct. Since the sporozoites are



Portal field of the liver of a rabbit, showing india ink in lymphatics around bile ducts after injection of the dye into the wall of the common bile duct; × 450.

liberated from the oocysts by the action of the pancreatic juice, presumably below the entrance of the pancreatic duct into the duodenum, it seems very unlikely that the organisms could reach the intrahepatic bile ducts by traveling within the lumen of the intestines and the common bile duct against the stream and against the peristalsis. Owing to the uneven surface of the mucosa of the duodenum and that of the common bile duct, the distance from the point of liberation of sporozoites to the point of their destination is probably several times greater than the actual measurement would indicate, and the task of accomplishing this feat seems out of proportion to the size of the organism.

Histologic studies of the earliest lesions of coccidiosis of the liver after infection by mouth revealed that sporozoites are first discovered

in epithelial cells of the small-sized and medium-sized intrahepatic bile ducts, while the extrahepatic ducts become secondarily infected by schizonts liberated from the cells after the schizogony cycle. The primary infection of the distal end of the common bile duct and subsequent "contact infection" by schizonts moving up into the bile ducts of the liver could be excluded by the later appearance of the lesions in the extrahepatic bile ducts.

Since the epithelial cells of the extrahepatic bile ducts can be infected by schizonts and are commonly found to harbor such organisms in advanced stages of schizogony, it seems strange that the sporozoites, if they come from the intestines, should go up so much farther into the intrahepatic bile ducts before they penetrate into epithelial cells.

All these considerations make it rather improbable that the sporozoites infect the intrahepatic bile ducts by direct emigration from the duodenum through the common bile duct.

The successful infection of the right lobe of the liver after ligation of its extrahepatic duct and subsequent infection of the animal by mouth demonstrated that occlusion of the bile duct does not prevent the sporozoites from reaching the intrahepatic bile channels. While the outcome of these experiments presented circumstantial evidence of the probability of another mode of infection, it was proved by other experiments that liberated sporozoites injected into a mesenteric vein can establish themselves in epithelial cells of intrahepatic bile ducts.

Although the possibility of this mode of infection had been considered by some authors,[2] it was thought to be improbable, the main reason being that coccidiosis of the liver is a disease of the biliary epithelium, which has no apparent relation to the vascular system of the liver. However, in studying the blood supply of the periportal fields, one can easily find capillary blood channels in the vicinity of bile ducts from which actively moving sporozoites can easily reach the biliary epithelium. It is certainly not inconceivable that sporozoites, endowed with motility and directed by chemotaxis, could digress from such capillaries through the tissue and penetrate the bile ducts from without. It is perhaps of significance that the earliest lesions are found in the small bile ducts and precapillary biliary channels, which possess only a delicate basement membrane or none at all; also the marked infiltrations of the portal spaces in very early infections, which seem out of proportion to the slight infestation of the bile ducts, perhaps finds an explanation in the temporary presence of these parasites in the tissues of the periportal fields.

For technical reasons it seemed impossible to solve the problem whether or not lymphatics play any rôle in the transportation of sporozoites from the intestines to the liver in any direct way; circumstantial evidence, derived from experiments with india ink, however, speaks

against the probability of lymphatics being the portal of entry into the liver for sporozoites liberated in the intestines.

CONCLUSIONS

Sporozoites of Eimeria stiedae reach the liver from the intestines by way of the portal radicals.

This was demonstrated experimentally by: (1) morphologic studies of the earliest lesions after oral infection; (2) exclusion of the biliary route by ligation of the extrahepatic bile duct of one of the lobes of the liver, subsequent to which oral administration of oocysts was nevertheless followed by infection of all the lobes of the liver; (3) coccidiosis of the biliary tract after injection of liberated sporozoites into a mesenteric vein.

Puncture of the gallbladder and examination of the bile for oocysts appear to be the most reliable method for determining past or present coccidial infection; biopsy of hepatic tissue alone is not satisfactory, unless the process is still active and diffusely scattered throughout the liver.

ANGIOMATOUS MALFORMATIONS OF THE BRAIN

REPORT OF TWO CASES OF ANGIOMA RACEMOSUM

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In the past few years widespread interest has been aroused in the subject of blood vessel tumors of the brain, especially since the publication of the monographs by Lindau [1] (1926) and by Cushing and Bailey [2] (1928). The latter authors divided these tumors into the hemangioblastomas, which have been dealt with especially by Lindau,[1] and the angiomatous malformations, of which a considerable number of cases have been reported (Buckley,[3] Dandy,[4] Nielson,[5] Frets,[6] Parkes Weber,[7] Rühl,[8] Sillevis Smitt,[9] Roussy and Oberling,[10] Stewart and Ashby [11] and Holmes [12]). The work of Marque and Dimitri [13a] has shown the possibility of recognizing the vascular tumors of the brain by roentgen examination. Cases thus diagnosed have been reported by Parkes Weber,[7] Sillevis Smitt,[9] Moore,[14] Krabbe,[15] Krabbe and Wissing,[16] Vincent and Heuyer,[17] Laignel-Lavastine, Delherm and Fouquet,[18] Uiberall,[19] Frigyér,[20] Pehu, Dechaume and Boucomont [21] and Ellis,[22] 16 cases in all.

From the Department of Pathology, Cook County Hospital; R. H. Jaffé, M.D., director.

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17. Vincent, C., and Heuyer, G.: Rev. neurol. **1**:509, 1929.
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19. Uiberall, H.: Ztschr. f. d. ges. Neurol. u. Psychiat. **124**:863, 1930.
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Because of the relative rarity of vascular malformations of the brain (Cushing and Bailey[2] list 16 cases among a series of 1,522 verified tumors of the brain; Dandy,[4] 16 cases in 600 verified tumors of the brain) it was thought worth while to report the following cases, in both of which the condition was discovered at postmortem examination. These cases occurred in a series of 24 tumors of the brain among 4,100 autopsies.

REPORT OF CASES

CASE 1.—A white man, aged 39, was brought to the Cook County Hospital on May 15, 1930, in deep coma. His sister-in-law stated that he had been a "heavy drinker" in the past. For two weeks before entrance he had been complaining of headache. During this time he had had two slight attacks of unconsciousness. Two days previously he again became comatose and had remained in that state.

On physical examination he was found to be fairly well nourished and in deep coma. His blood pressure was 140 systolic and 95 diastolic; the temperature, 104.4 F.; the pulse rate, 96, and respirations, 36. There was no sign of violence about the head or of bleeding from the ears, nose or mouth. His pupils were dilated and failed to react to light. The neck was rigid, and the extremities were slightly spastic. No definite paralysis could be found. The pharyngeal, corneal and abdominal reflexes were present, but all the deep reflexes were absent. He had a definite Kernig sign on both sides and a positive Brudzinski sign. Aside from moist râles throughout both lungs there were no other findings of note.

On spinal puncture, the fluid was bloody and under markedly increased pressure. The Wassermann reaction of the spinal fluid was negative.

The diagnosis arrived at was a cerebral hemorrhage due to spontaneous rupture of a blood vessel; bleeding into a tumor of the brain was also considered because the blood pressure dropped to 100 systolic and 80 diastolic after twelve hours. The patient remained in deep coma and died twenty-seven hours after admission.

Autopsy was made by Dr. R. H. Jaffé a few hours after the patient's death. The brain weighed 1,630 Gm. and had much loosely coagulated deep red blood about the left cerebral hemisphere and at the base about the infundibulum. The left temporal lobe was distinctly larger than the right, and a firm mass could easily be felt in it. The vessels of the pia mater over this lobe were much dilated and tortuous, somewhat entwined about one another, and their diameter varied from 6 to 12 mm. The general appearance was that of a tangled mass of worms.

On sectioning the formaldehyde-fixed brain (fig. 1), the left temporal lobe was found to be the site of a large blood-filled, multiloculated, cystic mass which laterally fused with the dilated vessels described in the leptomeninges, and was bordered on its medial and upper aspects by a 2 mm. strip of brain tissue, which separated the mass from the sylvian fissure. In sagittal diameter, the mass occupied most of the temporal lobe, while the vertical diameter was 30 mm. and the transverse diameter 40 mm. The center of the mass was formed by a roughly ovoid cavity 13.5 mm. in greatest diameter, around which were arranged numerous smaller irregular cavities, varying from 1 to 6 mm. in greatest diameters. The walls of these spaces were light gray and often very hard. Practically all of them were filled with dark red blood clots, which gave them the appearance of widely dilated, rather thin-walled blood vessels which were intermingled and intertwining.

The thin layer of brain tissue on the medial and upper sides of the mass was interrupted in the middle by a blood vessel 4 mm. in diameter, which was revealed to be the left middle cerebral artery. The lower portion of the left sylvian fissure

was distended by dark red clotted blood. The substantia grisea of the left hypothalamus, the medial portion of the left globus pallidus and the head of the left caudate nucleus were destroyed by a deep red hemorrhage, measuring on cross-section through the caudate nucleus 35 mm. in vertical and 25 mm. in transverse diameter. In the region of the caudate nucleus, the hemorrhage had broken into the left lateral ventricle, which was greatly dilated and filled by deep red coagulated blood.

Microscopic Study.—Left Temporal Lobe: The tumor was composed of a mass of wide blood vessels with distinct walls (fig. 2). These vessels involved the pia mater, where they were surrounded by recent extravasations of blood, and extended deeply into the brain itself. Inside the brain were small islands of nerve tissue from 1 to 2 mm. in diameter, between the vessels.

The diameter of the lumens and the thickness of the walls of these vessels were variable. Most of the vessels were filled with blood; a few contained recent thrombi with coral-like trabeculae of platelets and fibrin. Many of the vessels had

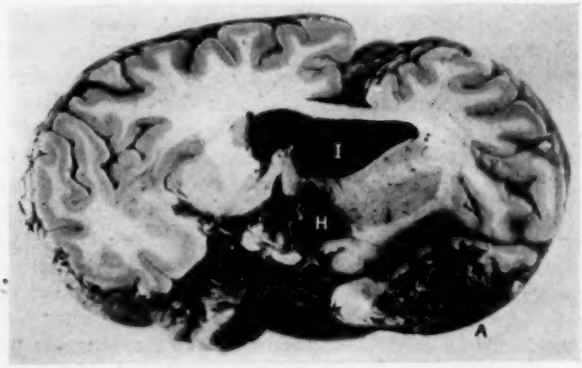

Fig. 1 (case 1).—A cross-section of the brain through the angioma (*A*) in the left temporal lobe; reduced from a magnification of × 0.66. *H* indicates the hemorrhage in the left hypothalamus; *I*, the intraventricular hemorrhage.

a distinctly differentiated wall, with a well developed internal elastic membrane, which was usually composed of several layers, and a media with muscle fibers and fine elastic fibers (fig. 2). There was only more collagenous tissue than is found in normal blood vessels. In sections stained by van Gieson's method, the yellow muscle fibers were surrounded and separated by much brighter red material. By an increase of this material, the muscle fibers became more and more scanty, to become finally completely replaced. The wall was then composed of dense connective tissue with few nuclei, and both the fine elastic fibers and the coarse membrane on the inside had disappeared. In these sclerotic walls calcium was deposited, first in the form of single small granules, later as coarse clusters and ultimately as splinters of bone.

The islands of nerve tissue between the vessels were rich in large glia nuclei and in capillaries, and there were small recent hemorrhages in these islands. The mass of vessels fitted into the brain without causing compression or displacement and with little reactive change about it. The latter consisted of an increased amount of microglia cells, especially of the Hortega type, as demonstrated by

Penfield's modification of the Hortega stain. There were no gitter cells about the tumor nor in the small islands of nerve tissue between the vessels of the tumor. Single wide and thick-walled vessels extended into the adjacent brain tissue, where they were surrounded by recent hemorrhages or by an increased number of oligodendroglial cells. There were many small hemorrhages in the form of streaks and rings in close proximity to the tumor.

Left Caudate Nucleus: There was a large compact hemorrhage surrounded by numerous smaller ones, the latter usually forming rings about the blood vessels.

Fig. 2 (case 1).—Angioma arteriale racemosum; Weigert's elastic tissue stain; reduced from a magnification of × 17. Note the well defined internal elastic membrane in every vessel, and the islands of brain tissue between the vessels.

Adjacent to the hemorrhage there was in one place a dense accumulation of polymorphonuclear leukocytes and mononuclear elements with very pale nuclei.

The essential anatomic diagnosis was: angioma arteriale racemosum of the left temporal lobe; large hemorrhage in the left caudate nucleus perforated into the lateral ventricle; intraventricular and intermeningeal hemorrhages; slight insufficiency of the mitral valve (rheumatic), and confluent bronchopneumonia in both lower pulmonary lobes.

The nature of the tumor is demonstrated by the photomicrographs. Figure 2 is a low power view of an elastic stain in which the tortuous nature of the blood

vessels is quite clear. It also discloses the fact that practically every vessel contains a fairly well developed internal elastic membrane. Because the great majority of the vessels have distinct elastic membranes, they are classed as arteries. Between the vessels, nerve tissue is demonstrable.

CASE 2.—This patient, a 46 year old white man, was brought to the Cook County Hospital on June 27, 1931, in coma and died nineteen hours after entrance. His wife stated that in the last few years he had been having infrequent epileptic seizures, as much as one or two years apart. Two weeks previously he had been brought home from work following such a convulsive seizure. He regained consciousness the next day, but did not seem so bright as before, complained of a stiff neck and severe continuous headaches and was restless. Two days before entrance he sank into a deep coma which persisted.

Physical examination disclosed the patient to be somewhat emaciated. His temperature was 103 F.; pulse rate, 128; respirations, 28, and blood pressure, 128 systolic and 74 diastolic. His pupils were small and reacted poorly to light. The head was held retracted, and the neck was rigid. Findings in the heart and lungs were negative except for a few crepitant râles at the bases of the lungs. The peripheral arteries felt somewhat sclerotic. The superficial reflexes were absent, the patellar reflexes sluggish and the achilles tendon reflexes normal. There were a moderately marked Brudzinski sign and a very marked bilateral Kernig sign.

Spinal puncture revealed a clear, light brown fluid under increased pressure, with a four plus Pandy reaction and 550 cells per cubic millimeter. Most of the cells were polymorphonuclear leukocytes. The fluid gave a strongly positive chemical reaction for blood. The only clinical diagnosis considered was acute leptomeningitis of undetermined origin.

Autopsy was performed about twelve hours after death. The brain weighed 1,390 Gm. The leptomeninges, especially over the convexity of the cerebellum, were covered with a thin layer of clotted blood which could be removed only with difficulty.

In the left parietal lobe, between the sylvian and rolandic fissures, was a somewhat irregular mass 5 cm. in anteroposterior and 4 cm. in vertical diameter, which was composed of tortuous intermingled blood vessels appearing like a clump of worms and varying from 0.5 to 7 mm. in diameter. This mass was bounded anteriorly by the rolandic fissure and inferiorly by the sylvian fissure, along each of which coursed a large, thin-walled venous trunk 7 mm. in diameter. Both of these veins had numerous communications with the wormlike mass of vessels and with the much enlarged veins in adjoining sulci. The large venous trunk in the rolandic fissure was tortuous. At its upper and medial end it emptied into the superior sagittal sinus as did a smaller, similar, roughly parallel venous trunk which was located posteriorly to the postcentral gyrus and extended upward in a winding manner from the tortuous mass of vessels described. At its lower end, the large trunk extended downward from the rolandic fissure and was joined by the similar venous trunk in the sylvian fissure near the anterior pole of the temporal lobe, from which point the combined trunk continued downward and medialward as the much enlarged middle cerebral vein. The branch in the sylvian fissure extended backward from the junction for a distance of 4 cm., then coursed in a winding fashion over the posterior portion of the temporal lobe backward and somewhat downward to reach the tentorium cerebelli, in which it ran for a distance of 2 cm. before communicating with the left transverse sinus.

The formaldehyde-fixed brain showed the following changes. On coronal sections (fig. 3), the wormlike mass of vessels in the left parietal lobe measured 2 cm. in vertical diameter, and from 3.5 to 4 cm. in transverse diameter. It extended about 5 cm. in an anteroposterior direction and was bounded laterally by the

wormlike mass of veins in the pia mater, and medially by the central ganglions. The blood-filled spaces forming the mass had numerous communications with the overlying pial vessels, varied from 0.5 to 11 mm. in greatest diameter, and were separated by small islands of brain tissue. About one third of the blood-filled spaces had calcified walls.

In all but the lateral 1.5 cm. the islands of brain tissue between the blood-filled cavities were the site of a diffuse hemorrhage. Medialward the adjacent portions of the body of the caudate nucleus and of the superior part of the anterior thalamic nucleus also contained a diffuse hemorrhage, which occupied an area 12 by 15 mm. on cross-section, and which bordered the left lateral ventricle. A 2 mm. opening at

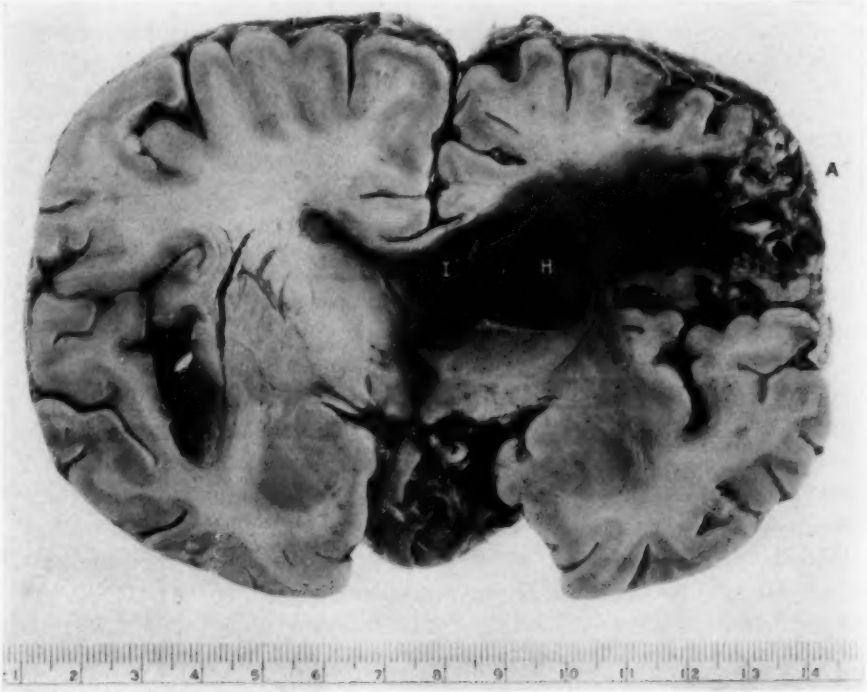

Fig. 3 (case 2).—A cross-section of the brain through the angioma (*A*) in the left parietal lobe; reduced from a magnification of × 1.25. *H* indicates hemorrhage in the left anterior thalamus and in the caudate nucleus; *I*, the intraventricular hemorrhage.

its most medial portion formed a communication between the hemorrhagic area in the thalamus and the dilated and blood-filled left lateral ventricle.

Microscopic Study.—Left Parietal Lobe: The tumor was composed of wide blood vessels with distinct walls, the thickness of which varied considerably. Some of these vessels had a relatively thick wall with a distinct internal elastic membrane and a media composed of muscle fibers, connective tissue and elastic fibrils. The intima often broke up into several layers, and intimal plaques were formed similar to those seen in arteriosclerosis. Other vessels had a less differentiated wall, which was essentially composed of connective tissue with single muscle

fibers and elastic fibers and stained red with the van Gieson stain. Many of the intimal plaques observed in some of the vessels were seen to have become calcified. The lumens of the vessels were filled with blood, and there was an occasional mural thrombus composed of blood platelets and white blood cells. Between the majority of the blood vessels there were small islands of nerve tissue, most of which were loosened and edematous and rich in glial nuclei, and most of which contained small hemorrhages. Larger hemorrhages were present between the vessels and in the more medial portions of the tumor.

The essential anatomic diagnosis was: Angioma venosum racemosum of the left parietal lobe; large hemorrhage in the left caudate and anterior thalamic nuclei, perforated into the left lateral ventricle; hemorrhage into the ventricles and between the leptomeninges; passive congestion of the lungs, liver and kidneys.

Figure 3, which is a view of the cross-section of the brain through the angioma, clearly shows the appearance of the tumor mass and the adjacent hemorrhage. In this illustration, islands of brain tissue can be seen between the vessels, especially in the lateral portion of the mass. In elastic stains of microscopic sections a varying amount of elastic fibers is found in closely adjacent vessels, some of which appear as definite arteries and others as veins.

COMMENT

Cushing and Bailey [2] divided the angiomatous malformations of the brain into three groups, namely, telangiectases, angioma venosum and angioma arteriale. The angioma venosum group is subdivided into simple varices, serpentine varices and racemose angiomas. The authors pointed out, however, that up to 1928 the nomenclature had often been confusing, a number of different names, such as angioma plexiforme or anastomoticum, varix arteriale or aneurysmaticus, rankenangioma and rankenaneurysm, having been used. Dandy [4] used the term arteriovenous aneurysm for the arterial type and venous abnormality for the venous type in most instances. Rühl [8] suggested the names hemangioma telangiectasis or hemangioma cavernosum. In the reports of Sillevis Smitt [9] and Roussy and Oberling [10] the name cavernous angioma is used. Vincent and Heuyer [17] spoke of cerebral venous aneurysm and Uiberall [19] of cirsoid aneurysm of the brain. Strictly speaking, the name cavernous angioma should not be used, since such a tumor is derived from capillaries. True cavernous angiomas of the brain do exist, and recent reports of such have been made by Jaffé [23] Hosoi [24] and Sehmisch.[25] I do not want to criticize any one terminology, but the great confusion of such a wide variety of names soon becomes apparent when one is searching for reports of cases belonging to this group. It is therefore suggested that the simple and clearcut classification of Cushing and Bailey [2] should be followed whenever possible.

23. Jaffé, R. H.: Arch. Path. **7**:44, 1929.
24. Hosoi, K.: Am. J. Path. **6**:235, 1930.
25. Sehmisch, W.: Virchows Arch. f. path. Anat. **277**:431, 1930.

Following this scheme, the type of tumor herein described would be classed under the grouping of angioma racemosum. The first 1 with a definite internal elastic lamina in most vessels would be called an angioma arteriale racemosum, while the second, in which most of the vessels appear as veins, can be listed as an angioma venosum racemosum. Grossly, the 2 tumors offered little in their appearance to allow a differentiation. The first tumor was somewhat more resistant to cutting owing to the greater amount of calcification.

In classifying a vascular tumor of the brain, the presence of a bruit during life or of visible pulsation at operation stamps it as arterial. Lacking this definite information at autopsy one is forced to rely on the histologic appearance of the vessels. That the clinical differentiation is not always satisfactory is brought out by an important case reported clinically by Isenshmid [13b] and pathologically by Herzog [13b] in which a bruit had been present for sixteen years, and in which the vessels were found microscopically to be veins.

At postmortem examination, as Cushing and Bailey [2] admitted, it is often impossible to distinguish arteries and veins in such tumors. Cushing and Bailey expressed the belief that both arteries and veins are usually present, but in some instances all the vessels may be veins. They also admitted that an audible bruit heard during life over such a venous tumor may have been due to an arteriovenous fistula. One of their patients (case 5), a girl in whom at the age of 4 a venous angioma was exposed at operation, at the age of 11 complained of a buzzing noise in her head. No bruit was audible on auscultation, but the buzzing noise suggests the possible formation of a fistula between the arteries and veins. Rühl [8] stated that most racemose angiomas of the brain are classed as arterial, but that this is often incorrect, as the vessels are mainly veins with thickened walls due to growth of the tumor. Stewart and Ashby [11] stated that the vessels in the case which they reported were neither normal arteries nor veins, histologically. Holmes [12] injected carmine gelatin into the carotid artery of his specimen and found that most of the vessels of the angioma were red. This, however, did not stamp the vessels as arteries, but proved that they communicated with the carotid artery. In the presence of an arteriovenous communication, vessels which originally were veins could become filled with the gelatin mass.

In this connection it is interesting to note the report of a case and the opinions expressed by Schloffer.[26] A 21 year old man had a mass on the scalp which clinically and histologically was diagnosed as angioma arteriale racemosum, which had been present for eight years and had

26. Schloffer, H.: Deutsche Ztschr. f. Chir. **225**:339, 1930.

been growing slowly. The tumor was excised and the carotid artery ligated, but a recurrence resulted after three years. Again it was removed, this time by galvanocautery, and all the main arteries of the scalp were ligated. A second recurrence took place three months later, but the tumor no longer was pulsating and arterial in nature. It was soft and cushion-like and on microscopic examination appeared mainly like a hemangioblastoma in which there were many thin-walled veins scattered throughout. This author believed that the clinical and histologic changes were due to the fact that the mass in the scalp was no longer in direct communication with the larger arterial trunks. This supported his view that an angioma arteriale racemosum is not a true tumor nor a completely preformed congenital arterial anomaly, but a mass of venous channels which have become arterialized because of an abnormal arteriovenous fistula. When the fistula was removed, in the case he reported, the vessels regrew in their original form as veins.

That angiomas of the type described here are not true tumors, but rather angiomatous malformations, is clearly shown in both my cases. The distinguishing features are lack of new formation of blood vessels or of vasoform tissues and the presence of islands of nerve tissue showing gliosis between the vessels. Cushing and Bailey [2] stressed the importance of these islands of nerve tissue in deciding that these malformations are congenital. Most authors, however, fail to mention them. Only the reports of Buckley,[3] Rühl [8] and Stewart and Ashby [11] take cognizance of them.

Undoubtedly the malformation occurs early in fetal life, since it usually, as in my cases, fits into the brain with little or no displacement of the surrounding tissue. This conception of a congenital malformation is favored by the fact that many venous angiomas have been described in children. Parkes Weber [7] mentioned a case associated with convulsions since birth and another in a girl of 6 who had epilepsy from the time that she was 14 days old. Other cases with incidence of symptoms before 6 months of age have recently been reported by Laignel-Lavastine, Delherm and Fouquet [18] (at 1 month), Vincent and Heuyer [17] (at 6 weeks), Sillevis Smitt [9] (at 3 months), Rocke [27] (at 3½ months) and Schaefer [28] (at 4 months). In one of the cases cited by Cushing and Bailey [2] (case 5) a child of 4 had fulness in the temporal region and exophthalmos at birth. The case with the longest history was that of a man of 42 (reported by Frigyér [20]) who had had symptoms since early childhood. In all, there are reports in the recent literature of 19 patients whose symptoms began as early as 6 years of age.

27. Rocke, J. M.: Proc. Roy. Soc. Med. **25**:793, 1932.
28. Schaefer, W.: Monatschr. f. Kinderh. **50**:35, 1931.

As yet there is no report of an angioma racemosum which was present in two successive generations of the same family. Kufs,[29] however, related an interesting familial incident in which the finding of multiple cerebral telangiectases in the brain of an 81 year old man cleared up the diagnosis of the cerebral condition from which his 43 year old daughter had been suffering for twenty-six years (facial paralysis, paresthesia, tinnitus aurium, diplopia, all without progression). The daughter was believed to have had hemorrhages from similar telangiectases.

The fact that many cases are not discovered until adult life seems to speak against their congenital origin. But the probability is that with the formation of an arteriovenous fistula (perhaps due to trauma or pressure) they become gradually larger and thus cause symptoms for the first time. That trauma may be the causative factor in the formation of such a fistula outside the cranial cavity is well known. Of interest here is the history which Stewart and Ashby [11] related. When their patient was 19 years old she received a blow on the head. Sometime afterward she noticed an enlarged group of veins on her forehead which pulsated with the cervical arteries. Two years after her injury she began to have severe headaches, and within the next few years other cerebral symptoms developed. As mentioned before, the authors stated that the vessels of this cerebral angioma ressembled neither true arteries nor veins; they may most probably be interpreted as arterialized veins.

If the idea that such angiomas have enlarged after the formation of fistula and have thus first caused symptoms in adult life is considered to be correct, then the supposition is strongly advanced that these angiomas are all originally venous, but become arterialized with the aid of the increased pressure through the abnormal communication. This is suggested by the histologic appearance in my second case, in which the vessels can be interpreted as arterialized veins with thickened walls and imperfectly formed elastic membranes. In the first case, in which the vessels have thicker walls, many of them appear to be true arteries. Here, however, the calcification is greater, which suggests that the longer the high arterial pressure acts on the veins, the more arterialized and calcified they become. It is not denied, however, that some of the vessels of such angiomas are arteries from the start, though the majority of them are merely arterialized veins.

The diagnosis of tumors of the type described here is often difficult during life, and many are recognized only at operation. The presence of a facial nevus is suggestive, but not by any means conclusive, of a similar blood vessel abnormality of the brain. If a person with a facial nevus has contralateral jacksonian epilepsy or paralysis, the diag-

29. Kufs, H.: Ztschr. f. d. ges. Neurol. u. Psychiat. **113**:651, 1928.

nosis of angioma of the brain is very probable. Other neurologic symptoms are often present. The presence of a cerebral angioma can often be verified by roentgenologic examination. Twenty-one of the cases found recorded in the recent literature occurred in patients with facial nevi. All but 1 of the patients had definite neurologic symptoms, and the remaining patient had eye findings which directed attention to his cerebral condition. Fourteen of these patients had typical roentgenologic findings, while 1 diagnosis was verified by operation and 1 by autopsy. Another case was partially verified by encephalogram, and 4 had only the presence of the facial nevus and the neurologic symptoms to establish the diagnosis.

Nine additional cases presented definite neurologic symptoms without the presence of facial nevi; 2 of these cases were verified by radiology, 1 by operation, 1 by both operation and autopsy and the remaining 5 by postmortem examination. It is needless to say that in many instances a roentgenogram of the skull was not taken, either through lack of time or through failure to suspect such a lesion. Had roentgen pictures been taken in the other cases mentioned, typical shadows would have been found in many of them. There were, however, 4 instances reported, out of the entire 30 cases, in which the roentgenologic findings of the skull were negative.

The appearance of the roentgen shadow is worth mentioning. The shadow is not uniform, but is described as being wavy and gyriform (Krabbe and Wissing [16]), scalloped and latticed (Vincent and Heuyer [17]) or serpentine (Frigyér [20]). Pehu, Dechaume and Boucomont [21] spoke of double-contoured lines, and Uiberall [19] calls the shadow "branched in double-contoured stripes"; he emphasized the double contour effect, which is due to the shadow of calcified vessels. Undoubtedly both of the angiomas reported here were calcified enough to cast roentgen shadows.

In addition to the 16 cases in which the roentgen shadows were similar to those described, it is worth mentioning that Cushing and Bailey [2] were aided in the diagnosis by a ventriculogram (case 12), and that Schaefer used an encephalogram as a helpful diagnostic procedure.

A frequent combination which has not been stressed previously is that of a facial nevus and an angioma of the occipital lobe (demonstrable by radiology) on the same side as the nevus. Of 14 patients with facial nevi and typical roentgen shadows, 7 had the shadows only in the occipital lobe, and 4 more had shadows both there and elsewhere. In only 3 were angiomas not found in the occipital lobe. Of the 4 cases which Krabbe and Wissing [16] reported, 3 had facial nevi and occipital lobe shadows. The patient without a cutaneous nevus had the angioma in a parietal lobe.

SUMMARY

Two cases of angioma racemosum discovered accidentally at postmortem examination are reported. One is diagnosed as an arterial and the other as a venous angioma on histologic grounds. These tumors are believed to be congenital malformations which are originally venous and which tend to become arterialized following the formation of an arteriovenous fistula. Both patients died from cerebral and intermeningeal hemorrhage.

NOTE.—Since this paper went to press articles by Brock and Dyke,[30] Croot [31] and Cornil and Mosinger,[32] reporting similar angiomas, have come to my attention.

30. Brock, S., and Dyke, C. G.: Bull. Neurol. Inst., New York **2**:247, 1932.
31. Croot, J.: Guy's Hosp. Rep. **82**:136, 1932.
32. Cornil, L., and Mosinger, H.: Ann. d'anat. path. **9**:955, 1932.

THE ANATOMIC LESIONS OF FATAL MERCURIAL INTOXICATION FROM SALYRGAN

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About six years ago reports of a new, nonirritating mercurial, called salyrgan, appeared, showing that this drug is followed by fewer toxic manifestations than certain other mercurials. Although the impression of the lesser toxicity of salyrgan is probably justified, the following report concerns a patient with congestive heart failure who received this mercurial diuretic shortly before death, and who showed definite anatomic signs of mercurialism at necropsy.

Andrews [1] has reported a case in which severe toxic symptoms were observed, and Wolf and Bongiorno [2] attributed a death to injection of salyrgan, but no necropsy was made. Tarr and Jacobson [3] made anatomic studies of thirty patients who had received injections of salyrgan and were able to find in but one any condition that was suggestive of mercurial damage to the kidney.

REPORT OF CASE

A white man, a physician, 59 years of age, was admitted to the hospital on Aug. 18, 1932, complaining of shortness of breath and swelling of the feet and of the abdomen. The family history was irrelevant. He had never had any of the common infections of childhood, and there was no history of pneumonia, typhoid or rheumatism. His family physician said that the patient was nervous, and that he had had a slight cardiac enlargement, but an always rhythmic heart beat, and that on several occasions he had had an apical presystolic and late diastolic murmur.

When first seen he was acutely ill, with dyspnea and orthopnea, cyanosis of the lips and swelling of the abdomen and legs. The eyegrounds showed moderate sclerosis. There was marked arterial pulsation in the neck, with slight venous fulness. Absence of fremitus in the right axilla and the lower right side of the back, with a flat percussion note, and absence of breath sounds were noted. The apical impulse was seen and felt in the sixth left intercostal space and anterior axillary line, with a rate of 64. Auricular fibrillation was present. The sounds at the apex were of poor quality, and the second sound was not heard well. There was a soft systolic murmur at the apex, and at the aortic arch there were both a systolic murmur and a distant diastolic murmur. The blood pressure was 180 systolic and

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1. Andrews, C. T.: Lancet **2**:131, 1931.
2. Wolf, I. J., and Bongiorno, H. D.: Canad. M. A. J. **25**:73, 1931.
3. Tarr, L., and Jacobson, S.: Arch. Int. Med. **50**:158, 1932.

70 diastolic. The liver was felt 3 fingersbreadths below the right costal margin, and was firm and tender. Evidence of ascites of moderate degree was present.

The blood showed a negative Wassermann reaction; a hemoglobin content of 95 per cent; a white blood cell count of 8,300, of which 71 per cent were polymorphonuclears; 107 mg. of urea, 7.2 mg. of uric acid, 1.88 mg. of creatinine and 115 mg. of sugar per hundred cubic centimeters.

The urine had a specific gravity of 1.022 and contained 0.25 Gm. of albumin per liter, a rare hyaline cast and no blood corpuscles.

An electrocardiogram revealed complete heart block. An outside physician reported that an electrocardiogram showed complete heart block before the patient had received 35 grains (2.07 Gm.) of digitalis.

On Aug. 19, 1932, the patient was placed on restricted fluids and soft diet. Intravenous injection of 1 cc. of salyrgan was followed by a large output of urine. The patient felt and looked better. Four days later 1.5 cc. of salyrgan was given in the morning. Shortly afterward the patient became irrational and increasingly dyspneic, coughed, and raised small amounts of blood-streaked sputum. The temperature was 102 F.; the pulse rate, 110, and the respiration rate, 35. Subcrepitant râles were heard anteriorly over the chest on both sides. There was no urinary response. That evening the patient complained of dyspnea and abdominal cramps. The following day he lapsed into coma, and pulmonary edema increased. The temperature was 102 F. The left leg was larger than the right. The blood showed a urea content of 117 mg. per hundred cubic centimeters, and the urine showed from 2 to 3 red blood cells per high power field. The next day the temperature rose to 105 F., the pulse rate to 120 and the respiration rate to 35. The blood pressure fell, and the patient died gradually of circulatory failure.

The necropsy, one and a half hours after death, showed swelling of the left lower extremity, with edema of the ankles; 500 cc. of clear yellow fluid was found in the right pleural cavity and 200 cc. of similar fluid in the left pleural and peritoneal cavities. The serosa of the gastro-intestinal tract was congested throughout.

Emboli were found in the pulmonary artery with hemorrhagic infarcts in the lower lobes of both lungs.

The heart was enlarged, weighing 465 Gm. In the upper third of the left descending coronary artery were found advanced arteriosclerosis, ulceration and thrombotic formation, though a complete anatomic occlusion of the vessel at this point could not be demonstrated. No fresh areas of myomalacia and no gross scars were found in the myocardium. The cardiac valves, except for the aortic cusps, which were slightly thickened and grown together for about 1 mm. at their junction, showed no macroscopic lesions.

The kidneys were normal in size, but unusually firm in consistency. Their capsules stripped with ease, leaving a surface that was smooth, with no scars or hemorrhages.

The liver showed a moderate degree of passive congestion and fatty infiltration.

The stomach contained 100 cc. of bloody fluid. Throughout the entire gastro-intestinal tract there was severe hemorrhagic infiltration of the mucosa. The process was most severe in the colon, especially in its descending portion and in the sigmoid flexure, where a gray, necrotizing diphtheritic membrane was found covering the mucosa.

The anatomic diagnosis including the results of microscopic examination was: general arteriosclerosis with cardiac hypertrophy; arteriosclerosis of the coronary and the pulmonary arteries; chronic infectious endocarditis, healed; slight stenosis and slight insufficiency of the aortic valves; hypertrophy and dilatation of the

heart; thrombosis of the veins of the left lower extremity and of the prostatic plexus; emboli of the pulmonary artery; infarcts of the lungs; acute fibrinous pleuritis; pulmonary emphysema; apical healed tuberculosis; acute hemorrhagic enteritis; parenchymatous degeneration of the kidney; acute catarrhal cystitis; hypertrophy of the urinary bladder; bronchopneumonia, and mercurial intoxication.

Microscopic Examination.—Bowman's spaces of many of the renal glomeruli were distended. These were either empty or filled with a small quantity of pink-staining granular material. Occasionally a few pale erythrocytes were seen. The

Fig. 1.—The lesions in the kidney.

tufts of some glomeruli and the parietal epithelium of others were distinctly swollen. Many of the capillaries in the tufts were distended and filled with red blood cells. Here and there in the interstitial tissue small focal collections of lymphocytes were found. The capillaries of the cortex were congested. Some of the convoluted tubules were dilated, and their epithelium varied from a flat to a moderately high cuboidal type with an acidophilic, granular cytoplasm. The nuclei were either large and round and vesicular or small and pyknotic. Complete necrosis and desquamation of many epithelial cells were seen. The lumens of many tubules contained a finely granular, sometimes stringy, pale pink-staining material. Calcium concretions and fatty degeneration were not noted. The arterioles showed a moderate thickening of their walls, with areas of hyaline degeneration (fig. 1).

In the intestines, most of the epithelial cells lining the gland spaces had lost their cell outlines, and their nuclei were missing. The cytoplasm was granular and acidophilic. The pale-staining skeletal outlines of the glands and villi were all that remained of the mucosa in some areas. Where the tunica propria was still intact a diffuse infiltration by acute and subacute inflammatory cells was found. The muscularis as well as the submucosa was diffusely infiltrated by acute inflammatory cells. The vessels of the submucosa were dilated and filled with red blood cells and leukocytes, and there were also marked edema and congestion of these tissues (fig. 2).

Fig. 2.—Necrosis of the mucosa of the colon, with submucous thrombosis.

Chemical Examination.—Samples of the intestine, kidney and liver were prepared for chemical examination (Dr. Alfred Goerner) with hydrochloric acid, and copper foil was placed in each sample for seventy-two hours. The copper was then removed and heated in a narrow glass tube. Minute globules of mercury condensed in the cool ends of the tubes containing the copper foil which had been in contact with the intestine and kidney, while none was found in that containing the copper which had been in contact with the liver. With iodine, the droplets formed the red iodide of mercury. Blank tests showed the absence of mercury from the reagents.

Since only a small quantity of salyrgan was given, this patient apparently possessed an increased susceptibility to the drug, a suggestion

supported by the evidence found by Andrews [1] in his case. In view of the increasingly widespread use of salyrgan and the numerous favorable reports from experimental and clinical studies of its action,[4] this case is of interest, since it supports the doubt held by some as to the absolute harmlessness of the drug by the actual demonstration in man of structural lesions due to the presence of mercury in the tissues.

SUMMARY

A case is described in which therapeutic administration of salyrgan led to the typical anatomic lesions of mercurialism, associated with mercury in the tissues.

4. Tarr and Jacobson.[3] Crittenden, P. J.: J. Pharmacol. & Exper. Therap. **46**:39, 1932. Petzal, E.: Deutsche med. Wchnschr. **52**:1651, 1926. Bernheim, E.: Therap. d. Gegenw. **65**:538, 1924. Grossman, M.: Schweiz. med. Wchnschr. **58**: 1249, 1928; Med. Klin. **21**:1730, 1925. Engel, K., and Epstein, I.: Ergebn. d. inn. Med. u. Kinderh. **40**:187, 1931. Johnstone, B. I.: J. Pharmacol. & Exper. Therap. **42**:107, 1931. Barker, M. H., and O'Hare, J. P.: J. A. M. A. **91**:2060, 1928. Agnew, G. H.: Canad. M. A. J. **18**:45, 1928.

PATHOLOGY OF BRONCHIECTASIS

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The frequency with which bronchiectasis is preceded by acute respiratory disease has been commented on by different authors.[1] Of particular significance are the figures published by Gladys Boyd[2] in a series of fifty-eight cases recently studied in the Hospital for Sick Children, Toronto. These figures with her comments follow:

Factors leading to the production of bronchiectasis

Bronchopenumonia	23
Recurring or chronic bronchitis	7
Measles and pertussis together	5
Pertussis alone	5
Measles	4
Influenza	4
Empyema	4
Tonsillectomy	2
Lung abscess	2
Cough, always	2

Bronchopneumonia, usually in repeated attacks, would appear, therefore, to be responsible for the largest number of cases. Probably its responsibility would appear even greater if it were possible to know the degree to which it was present in some of the other cases. The etiology of those cases attributed to lung abscess in uncertain. It is even debatable whether the abscess was the cause or secondary to the bronchiectasis. We are inclined to the former view.

Analyzing these figures further, the twenty-six patients who had conditions other than bronchopneumonia or bronchitis suffered, except the two with cough, from diseases in which one or both of these involvements usually occur. Empyema and pulmonary abscess are frequently preceded by pneumonia; the latter may follow tonsillectomy. In the

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1. (*a*) Clark, A.; Hadley, W. J., and Chaplin, A.: Fibroid Disease of the Lung and Pleura, London, C. Griffin & Co., 1891. (*b*) Findlay, L., and Graham, S.: Arch. Dis. Childhood **2**:71, 1927. (*c*) Kline, B. S.: Am. Rev. Tuberc. **24**:626, 1931. (*d*) McNeil, C.; Macgregor, Agnes R., and Alexander, W. A.: Arch. Dis. Childhood **4**:170, 1929.

2. Boyd, Gladys: Canad. M. A. J. **25**:174, 1931.

remaining eighteen patients, the bronchiectasis dated from acute infectious diseases often associated with acute bronchitis and followed by pneumonia. It is not improbable that some of the cases dating from an attack of bronchitis were complicated by more or less severe bronchopnemonia. In discussing this point, Findlay and Graham [1b] stated: "Not only in our own series, but also in those of other writers, a history is sometimes obtained that bronchitis was the starting point of the patient's malady. In our own series this was so in one case, but this patient was an infant, *at the time when the difficulty of differentiating between bronchitis and bronchopneumonia is well known.*" Boyd also observed that "most cases started before the age of two years." This lends additional support to the view that many of the cases of bronchitis were complicated by bronchopneumonia.

The evidence then that some form of acute respiratory disease marks the onset of bronchiectasis is so overwhelming that it cannot be lightly regarded, and the one thing in common, in my opinion, is an acute ulcerative bronchitis with resulting damage to the underlying supporting structures. Almost one hundred years ago, Stokes [3] of Dublin maintained that the starting point of all cases of bronchiectasis was bronchitis, a view which has been held by various observers since then. In 1921, Opie [4] and his co-workers published a most excellent and well illustrated book on the pathology and bacteriology of pneumonia following influenza, in which the early lesion of bronchiectasis is demonstrated to be an acute ulcerative bronchitis. To quote from their work: "When the epithelial lining of the bronchus is destroyed, coagulative necrosis of the underlying tissue occurs and may extend a variable distance into the bronchial wall, not infrequently penetrating into or entirely through the muscular layer. These changes furnish an explanation of bronchiectasis following influenza." They also reported finding ectatic bronchi lined by a modified or squamous type of epithelium. Similar observations were reported in 1929 by Ireland [5] and his co-workers from the Medical Department of the United States Army in the World War, and in the same year another excellent article appeared by McNeil, Macgregor and Alexander [1d] of Edinburgh.

While much of what I have to present is, therefore, not new, yet so little attention seems to have been paid to the findings of these

3. Stokes, W.: Treatise on the Diagnosis and Treatment of Diseases of the Chest, Dublin, J. Falconer, 1837.

4. Opie, E. L.; Blake, F. G.; Small, J. C., and Rivers, T. M.: Epidemic Respiratory Disease, St. Louis, C. V. Mosby Company, 1921.

5. Ireland, M. W.; Callender, G. R., and Coupal, J. F.: Pathology of Acute Respiratory Diseases, Medical Department of the United States Army in the World War, Washington, D. C., United States Government Printing Office, 1929, vol. 12.

authors that I wish to offer my own observations, hoping that the wider publicity of these views may lead to a clearer understanding of the pathologic process or processes underlying bronchiectasis.

Of the thirteen cases forming the basis of this study, eleven came to autopsy, while in the other two cases the left lower lobe was removed at operation. Though this series is small, there is a wide variation in the duration of symptoms, ranging from ten days to five and one-half years, and the study of the progress of the disease as revealed at different stages provides the explanation of the pathology of the long-standing chronic case.

While I do not at all suggest that at a given time in the development of the disease all cases of bronchiectasis show the same picture, as this must vary with the severity of the initial lesion, the degree of mechanical obstruction, the extent of the lung involved, the type and virulence of the bacteria present and the frequency with which the lung has been subjected to repeated attacks of bronchitis or pneumonia, at the same time I am impressed by the fact that the disease is a progressive one, and also that its several stages can be traced, with individual variations, from the initial lesion to the end-stage seen in old chronic cases.

Two main stages in the course of the disease may be recognized: (1) the stage of damage or destruction; (2) the stage of repair.

THE STAGE OF DESTRUCTION

The earliest lesion is not unlike that commonly seen in acute bronchopneumonia. This is shown in figure 1 *A* picturing a bronchiole in the lung of a 4 year old boy (case 1) who died ten days after the onset of acute purulent staphylococcic bronchopneumonia complicating typhoid fever. The small bronchiole is seen filled with a purulent exudate; one half of the epithelium has been destroyed, and although there is considerable polymorphonuclear infiltration of the wall, some of the muscle fibers remained intact. The surrounding alveoli are filled with exudate. Other bronchioles showed more extensive ulceration, some communicating with definite abscesses.

The wall of a dilated bronchus of a 6 week old infant (case 2) with a history of acute bronchitis and purulent bronchopneumonia, again of ten days' duration, is shown in figure 1 *B*. The destruction here has been more extensive, the bronchus being lined by a zone of necrotic material in which the original elements of the wall are no longer visible. Some of the surrounding alveoli are collapsed; others are filled with exudate.

The next step is shown in case 3, that of a 6 year old girl who died three weeks following the aspiration of a tooth during an epileptic seizure. At autopsy, the tooth was found blocking the lumen of the

main bronchus to the right lower lobe and was partially embedded in the swollen mucosa. The right lower lobe was the seat of a foul-smelling necrotizing pneumonia, in which some bronchi were widely

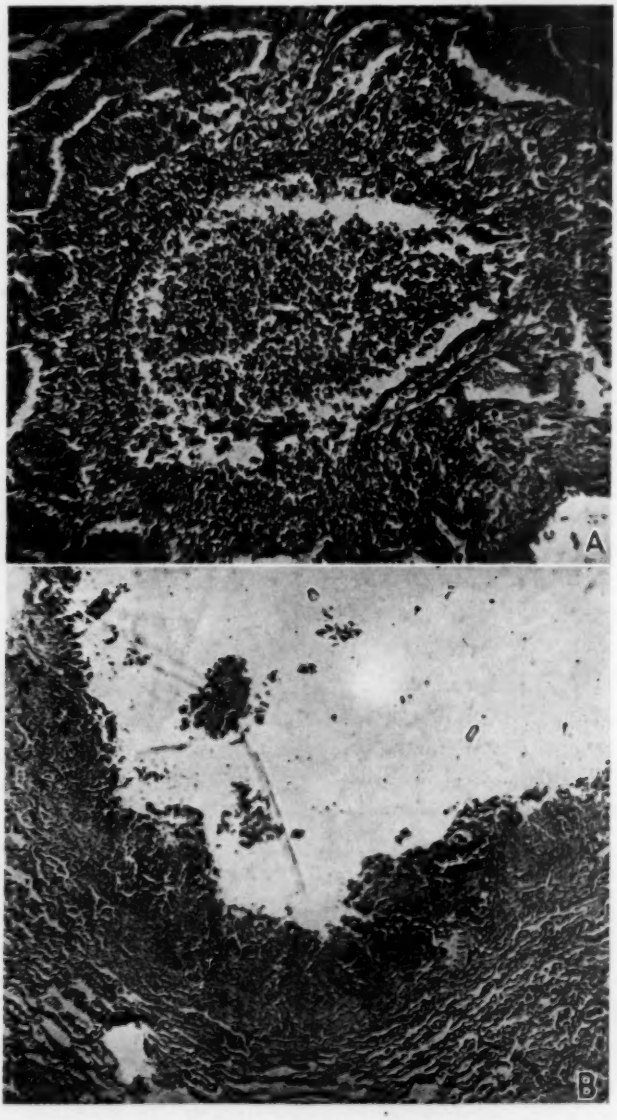

Fig. 1.—*A*, bronchiole and surrounding alveoli, showing early ulcerative bronchitis (case 1; duration ten days); × 60. *B*, wall of ulcerated dilated bronchus lined by necrotic material (case 2; duration ten days); × 36.

dilated. Figures 2 *A* and *B* show longitudinal sections of two of these dilated bronchi entirely devoid of epithelium. In *A*, necrotic pulmon-

ary tissue constitutes one side of the bronchial wall, while the other side of the wall is more clearcut and contains numerous dilated capillaries. This necrosis does not take place uniformly throughout the

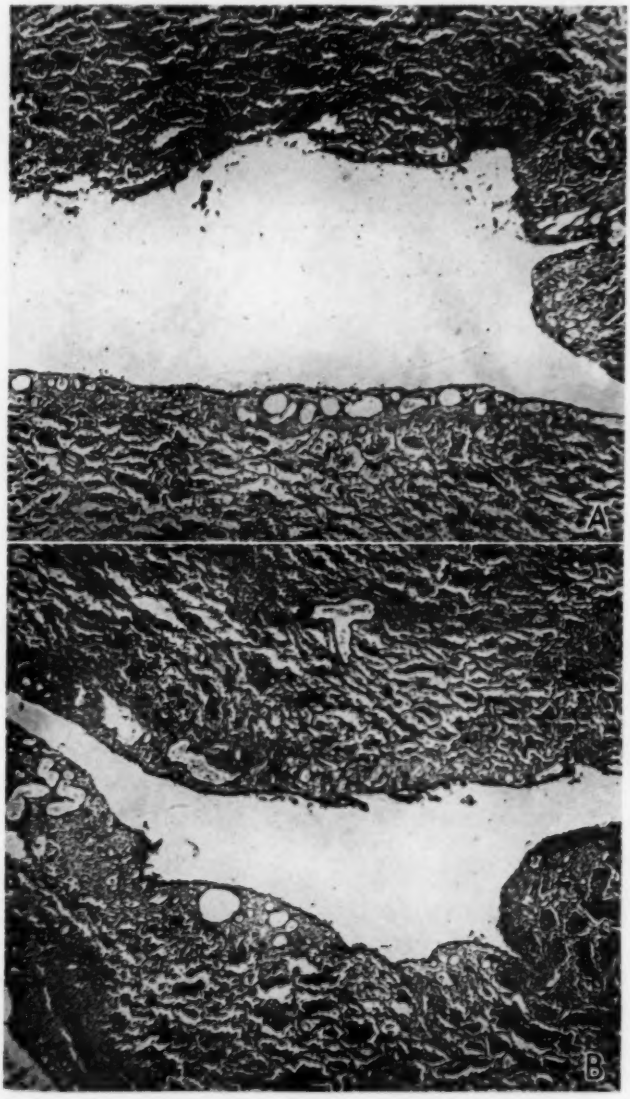

Fig. 2.—Longitudinal sections of two bronchi showing ulceration and fusiform dilatation (case 3; duration three weeks); × 36.

bronchus, and this, I believe, is one of the factors contributing toward the production of the fusiform or saccular dilatations. Another factor is the irregular distribution of exudate in the surrounding alveoli. In

B, the alveoli in the region of the greatest dilatation are shown collapsed and containing little exudate, while those surrounding the narrower portion of the bronchus are filled with exudate and have, therefore, less tendency to collapse.

A third factor in the production of irregular dilatation is illustrated in case 4, that of an infant 6 months of age who had had head-cold since birth, and who died three and one-half weeks after the onset of persistent cough and signs of lobar pneumonia. As Opie [4] and his co-workers pointed out, there frequently develop in the bronchial wall small fissures or tears which may extend through the entire thickness of the wall to the alveoli of the lung, and as the edges of these fissures separate the circumference of the bronchus is correspondingly increased. Such rents or tears are seen in figure 3 *A* and *B*, as well as epithelial destruction, loss of pulmonary tissue, bronchial dilatation and collapse of adjacent alveoli. One small vestige of epithelium, however, remains in *B*, and it is from such remnants that regeneration of epithelium subsequently takes place.

In case 5, that of a 5 year old boy, there was a history of whooping cough and a "cold in the chest" for four and one-half weeks, with short shallow respirations for three weeks preceding death. The microscopic picture is illustrated in figure 4 *A*. Again necrotic tissue lines the bronchus, the wall of which is composed chiefly of collapsed alveoli. This case also affords an illustration of the manner in which some of the smaller bronchi may become blocked with inspissated exudate (figure 4 *B*). Many of these passages have been plugged with stagnant exudate a sufficient length of time to allow the invasion of the latter by young fibroblasts arising from the connective tissue of the bronchial wall. That such plugging of the bronchial lumen is a factor in the production of bronchiectasis will be discussed under "Mechanical Obstruction."

In case 6, which occurred in a girl 2½ years old with symptoms of pulmonary tuberculosis of about six weeks' duration, the bronchiectasis proved to be a secondary development. This case also exemplifies the part played by mechanical obstruction in the development of bronchiectasis. In contrast to case 3, in which the obstructing agent was a tooth, and case 5, in which inspissated exudate plugged the lumen, the obstruction in this instance was situated *outside* the bronchus—a large caseous gland pressing against the bronchial wall. In addition to partial obstruction, the gland also had caused erosion of the bronchial wall, which allowed the softened contents of the gland to be discharged into the lumen. Before this had occurred, however, a secondary nontuberculous infection of the right middle and lower lobes had taken place, and since drainage from these lobes had been

blocked by the gland, extensive dilatation of the smaller bronchi had resulted. This is illustrated in figure 5. The view that the process is one of destruction rather than true dilatation is substantiated by

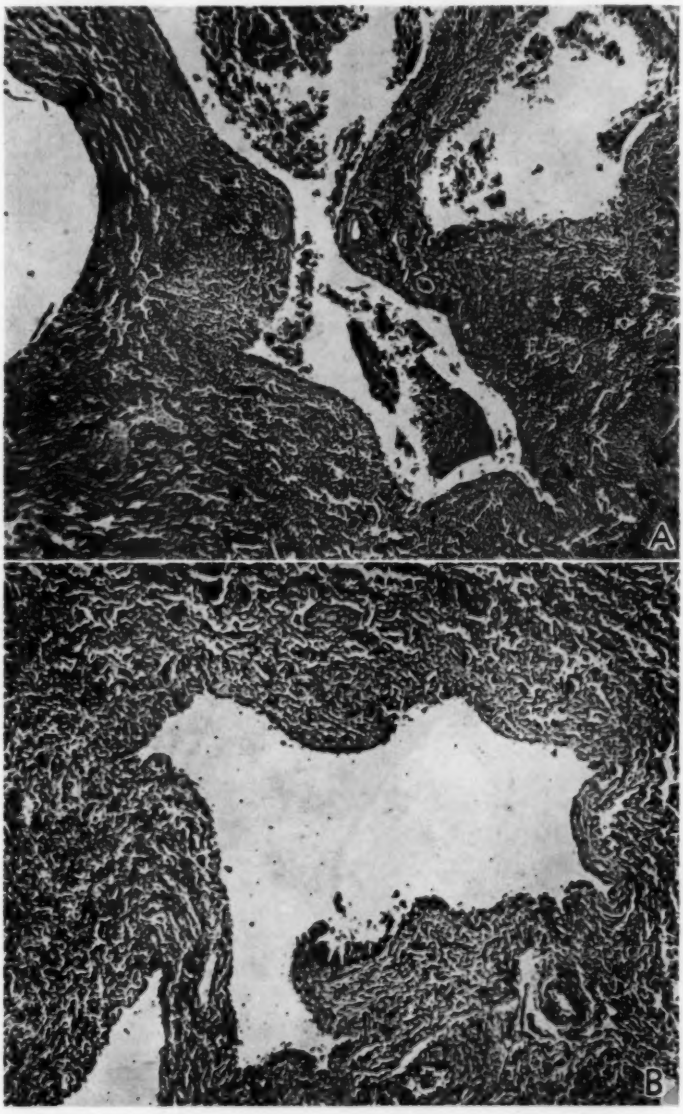

Fig. 3.—*A*, several ulcerated dilated bronchi (case 4; duration three and one-half weeks); × 36. *B*, ulcerated dilated bronchus with remnant of epithelium (same case); × 36.

the large size of the cavities as compared with the remaining pulmonary tissue.

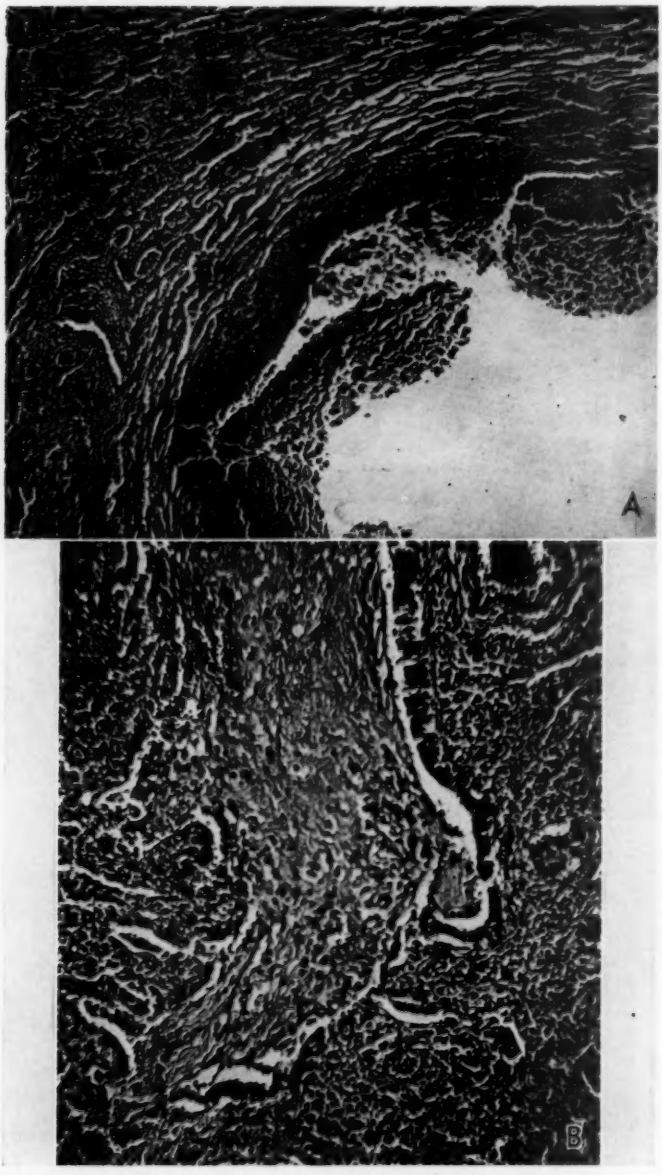

Fig. 4.—*A*, portion of ulcerated bronchial wall, the original structures of which are completely destroyed (case 5; duration four and one-half weeks); × 36. *B*, early organization of inspissated bronchial exudate, an important factor in preventing free drainage (same case); × 120.

In these six cases, the duration of symptoms had been less than six weeks, and while varying degrees of bronchial dilatation had been observed, *in no instance had there been any evidence of epithelial regeneration or of fibrosis of the intervening parenchyma.*

The process thus far described has been one of destruction of bronchial wall alone or of bronchial wall and adjacent pulmonary tissue. The subsequent changes are those of repair.

THE STAGE OF REPAIR

Opie [4] and his co-workers showed reparative changes occurring as early as the third week. In my series, however, little evidence of repair was noted until the sixth week, except for the early organ-

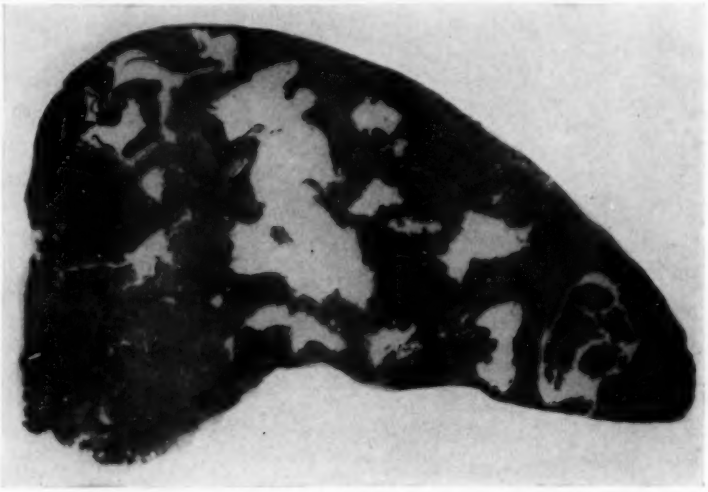

Fig. 5.—Extensive destruction of bronchial walls, together with pulmonary parenchyma (case 6; duration approximately five weeks); × 3.

ization of bronchial exudate seen in case 5, in which the symptoms were of four and one-half weeks' duration. While the process of destruction is measured in days or weeks, that of repair is measured rather in months or years, and although nature makes every attempt to repair the extensive damage, the end-result is most disappointing.

The first evidences of repair, with the exception noted, were found in case 7, that of a 4 year old girl who gave a history of whooping cough for six weeks, with pneumonia for one month. Figure 6 *A* shows purulent exudate filling a bronchus, the wall of which is devoid of epithelium save on one side where there is a low epithelial lining (fig. 6 *B*). Instead of a normal ciliated columnar epithelium, a modified epithelium approaching the squamous type has appeared. This, I think,

represents new epithelium arising from such epithelial remnants as seen in figure 3 *B*. This process of relining the bronchus with a new epithelium is usually preceded by the formation of a zone of highly vascular

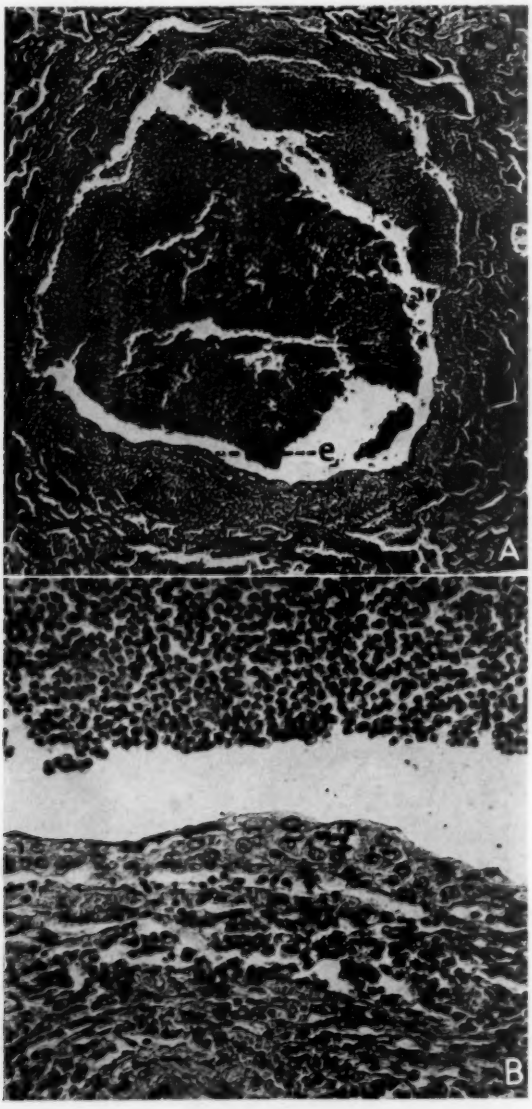

Fig. 6.—*A*, early stage in relining of ulcerated bronchus with modified epithelium (case 7; duration six weeks); × 36. *B*, details of new epithelium at *e* in *A*; × 240.

granulation tissue in the bronchial wall from which muscle and elastic fibers have wholly or partially disappeared. Experimental evidence of

such epithelial regeneration without regeneration of the other structures of the bronchial wall has recently been furnished by Adams and Livingstone.[6]

The transition from the stage of destruction to that of repair is illustrated in case 8, that of a 19 month old infant who had had a cough and otitis media for six and a half weeks and symptoms of pneumonia for one month before death. Space does not permit illustrations of all the changes found. These varied from partial loss of epithelium to complete destruction of all the original elements of the bronchial walls. In many instances, the latter were composed wholly of granulation tissue; in others, they were being relined by epithelium. A wall of granulation tissue is shown in figure 7 *A*, and it is over such granulation tissue that the new epithelium usually grows (fig. 7 *B*). In this instance, the new epithelium was of the squamous variety.

As repair goes on, the relining of these cavities continues until it is more or less complete. The lung in the gross may then have a honeycomb appearance. Microscopically, however, the individual saccular or fusiform dilated bronchi are lined not by naked granulation tissue but by a continuous sheet of epithelium. The relative size of some of these cavities is shown in figure 8 *A*, which represents pulmonary tissue from an infant of 11 months with a history of cough and head-cold for four and one half months (case 9). The exact duration of the bronchitis, bronchiectasis and bronchopneumonia found at autopsy could not be determined. Although there were no fibrous pleural adhesions and little fibrosis in the walls of these cavities, yet large epithelium-lined spaces representing dilated bronchi were conspicuous. Figure 8 *B* shows a portion of the partition between the two larger cavities seen in *A* with distinct epithelial lining. Here the underlying granulation tissue is still quite vascular and thickly infiltrated with round cells. The epithelium lining these dilated bronchi in some instances is of a modified type, but on the whole it approaches the normal ciliated variety (fig. 8 *C*).

A 6½ month old infant had a history of cough and failure to gain weight for five months, becoming acutely ill with fever and rapid, shallow, difficult breathing for twelve days before death. At autopsy, the lung showed evidence of acute bronchitis and bronchopneumonia superimposed on bronchiectasis of long standing (case 10). An idea of the degree of bronchiectasis may be gathered from figure 9 *A*. A few of the dilated bronchi show recent inflammatory change, in some instances ulcerative and probably coincident with the exacerbation of symptoms in the last twelve days. The great majority of the dilated bronchi, however,

6. Adams, W. E., and Livingstone, H. M.: Ann. Surg. **95**:106, 1932.

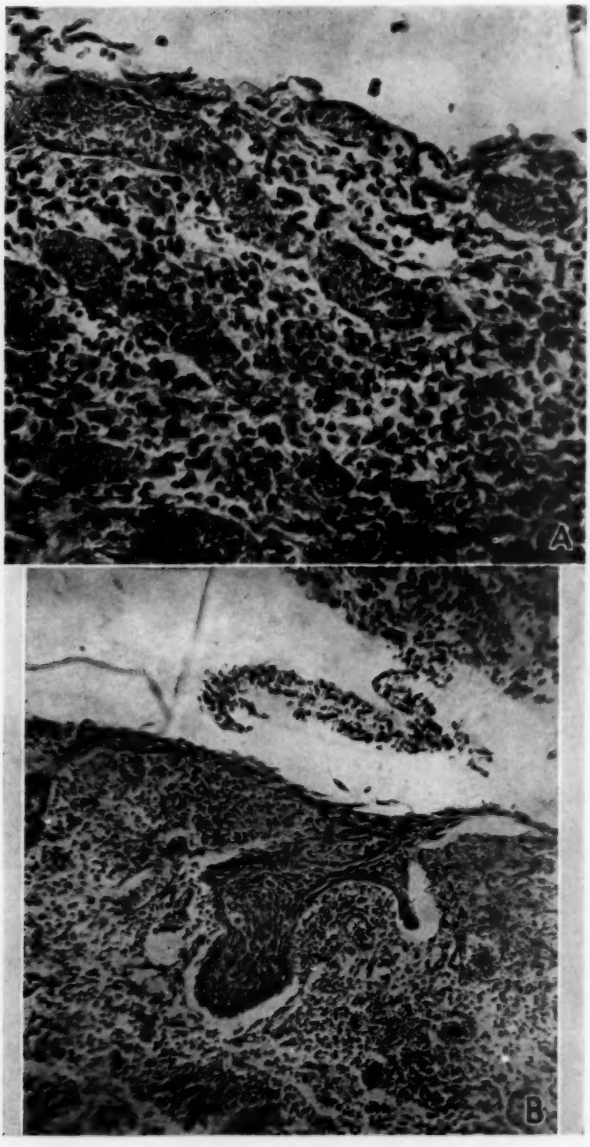

Fig. 7.—*A*, wall of bronchus lined by granulation tissue (case 8; duration six and one-half weeks); × 240. Note absence of muscle and elastic fibers. *B*, granulation tissue of bronchial wall becoming lined by squamous epithelium (same case); × 120.

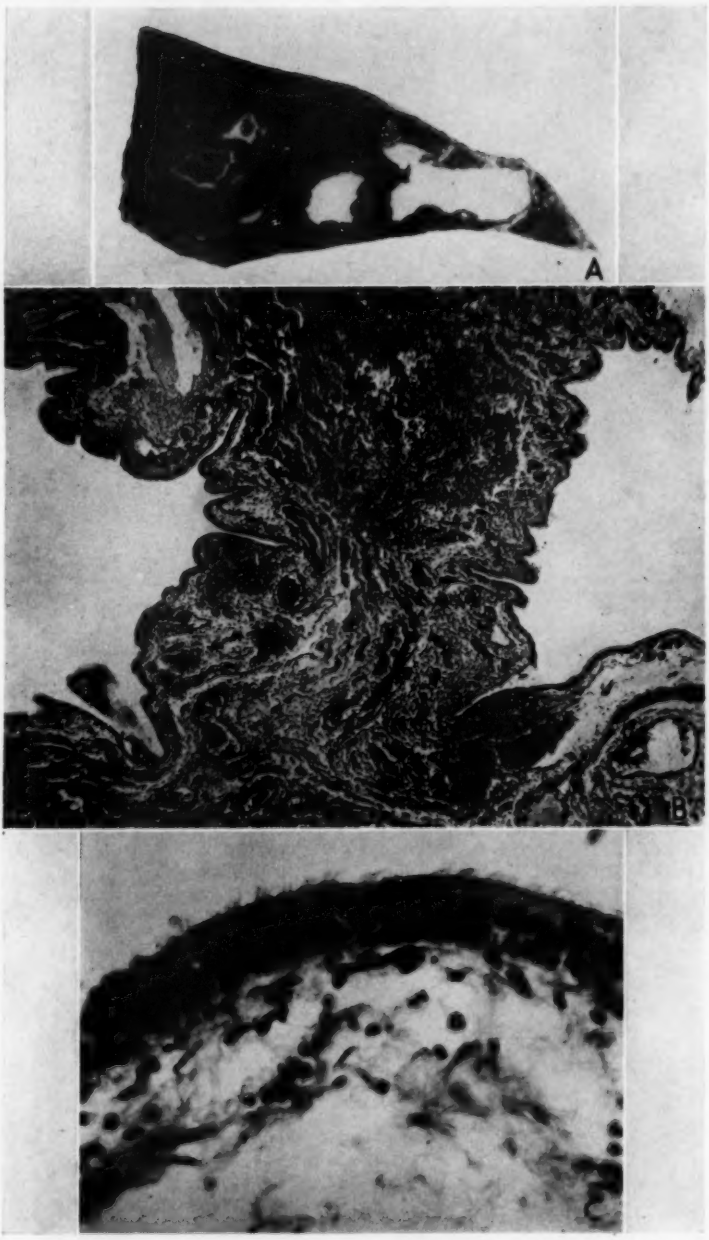

Fig. 8.—*A*, photograph of a microscopic section of a lung (case 9; duration four and one-half months ?); × 3. Note large size of bronchi, some filled with pus, others empty. The largest is immediately underneath the pleura and is completely surrounded by epithelium. *B*, higher magnification (× 36) of the partition between the two bronchi shown in *A*. Note the lining epithelium. *C*, the ciliated epithelium which was present in places; × 400.

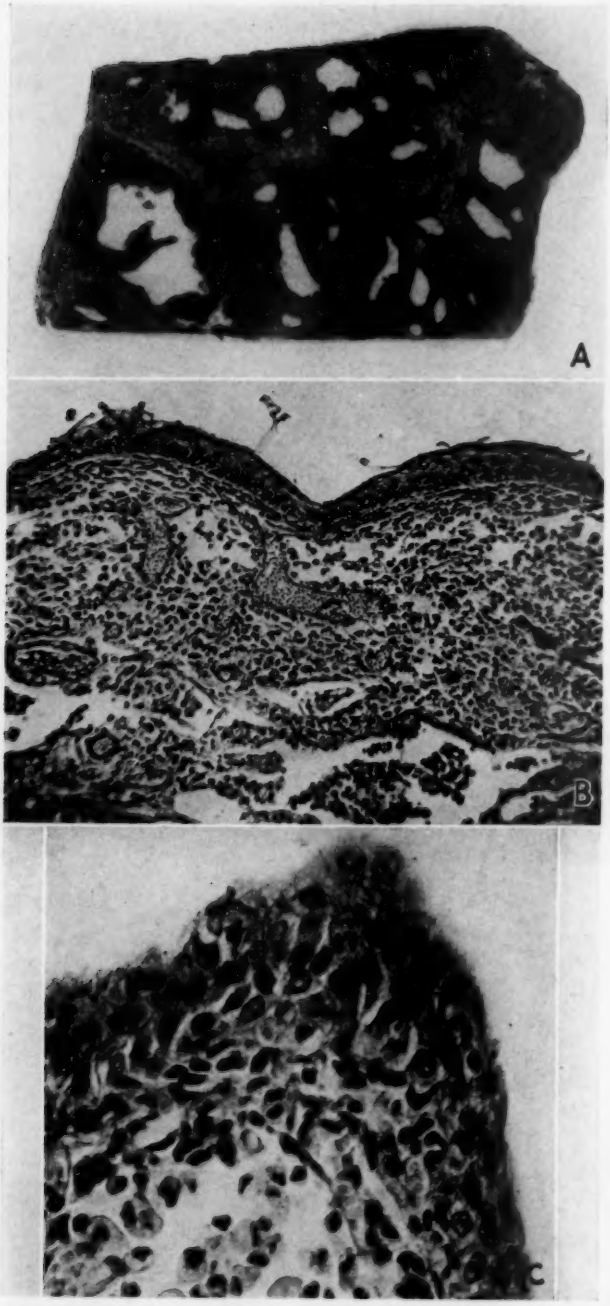

Fig. 9.—*A*, photograph of a microscopic section of a lung (case 10; duration five months); × 3. Practically all of these large bronchi are lined by epithelium. *B*, higher magnification (× 120) of bronchial wall shown in *A*. Here the epithelium approaches the squamous type. Note the underlying vascular granulation tissue and the absence of muscle and elastic fibers. *C*, new modified epithelium (same case); × 400. Note the mitotic figure.

have walls composed chiefly of more or less vascular granulation tissue and are lined by epithelium which closely approaches the squamous type (fig. 9*B*). The finding of occasional mitotic figures (fig. 9*C*) may be taken as another indication of the proliferation of these epithelial cells.

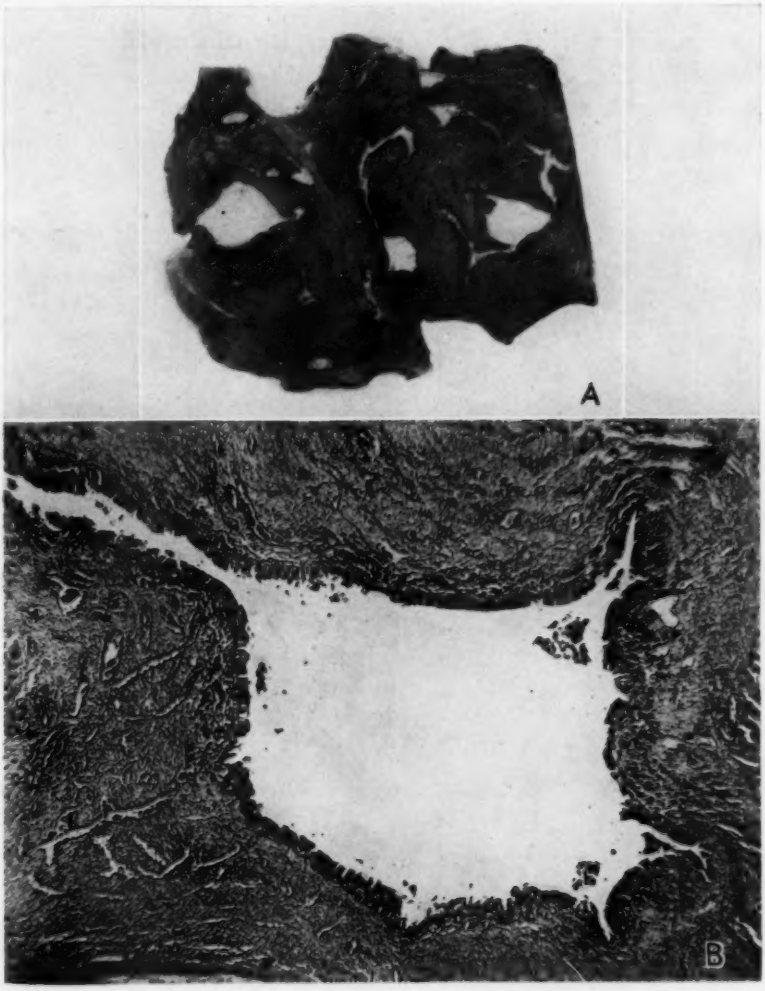

Fig. 10.—*A*, photograph of a microscopic section of lung (case 11; duration six and one-half months ?). Note the large size of the bronchi, the extensive fibrosis and the relative absence of alveoli; × 3. *B*, wall of bronchus composed of vascular fibrous tissue, devoid of muscle, and lined by nonciliated transitional epithelium (same case); × 36.

In case 11, the disease had advanced a step further. This was the case of an 8 month old infant with a history of a "rattle in the throat"

for six and one-half months and severe cough for four and one-half months. Whether the first symptom was an indication of bronchitis at that early date cannot be determined; the pulmonary changes were certainly of long standing. Figure 10 *A* shows a number of widely dilated but epithelium-lined bronchi separated by broad sheets of connective tissue in which little parenchyma remains (fig. 10 *B*). The epithelium here is of the columnar variety, but cilia could not be found. The subepithelial connective tissue contains numerous capillaries, but these are much smaller than those seen in the earlier stages of the disease, and the fibrous tissue approaches in density that shown in the next case.

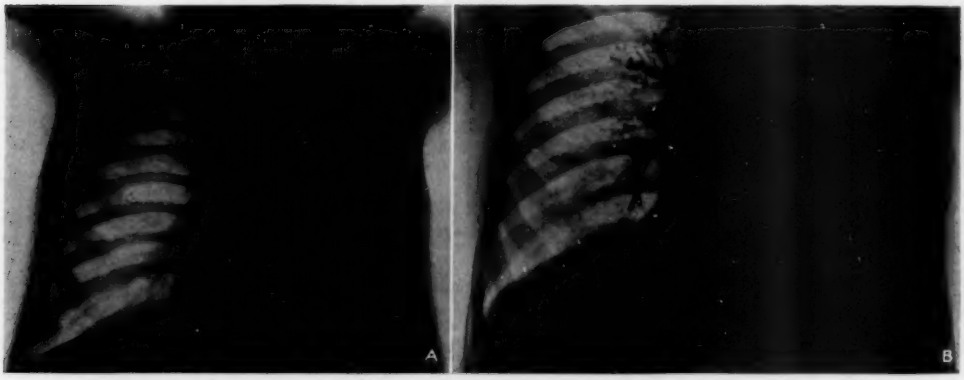

Fig. 11.—*A*, x-ray picture of chest (case 12) taken one week after the onset of primary pneumonia; *B*, x-ray picture of the chest taken two and one-half years later, when bronchiectasis was well established.

Case 12 was that of a girl who in July, 1929, at the age of 14 months, was admitted to the Hospital for Sick Children with acute pneumonia of the left lung of six days' duration. Previously she had been in good health. An x-ray picture of the chest taken on admission is reproduced in figure 11 *A*. The condition was thought to be empyema, but repeated attempts to aspirate pus were unsuccessful. The parents removed the child while she was still quite ill, one week after admission. Two and a half years later (December, 1931) she was readmitted because of chronic cough that had persisted since her original illness. The diagnosis now was chronic bronchiectasis of the left lower lobe (fig. 11 *B*). For the next two months various methods of treatment were employed, with only indifferent results. In February, 1932, about two years and eight months after the child's original illness, Dr. D. E. Robertson performed lobectomy of the left lower lobe. Old fibrous

adhesions bound the lobe tightly to the thoracic wall and diaphragm. After a short, somewhat stormy convalescence she made a splendid recovery and is now in excellent health.

The gross appearance of the lobe (fig. 12), with approximately the anterior fourth cut away, shows ragged fibrous pleural tags and widened bronchi, which end in saccular dilatations close to the periph-

Fig. 12.—Drawing of the left lower lobe of a lung removed at operation, two years and eight months after primary pneumonia (case 12).

ery of the lobe. The parenchyma has been replaced by dense connective tissue. An interesting feature of the picture is the presence of numerous transverse ridges in the bronchial walls. The significance of these will be discussed with the relation of fibrosis to bronchiectasis. Microscopically, all the dilated bronchi are lined by epithelium (fig. 13), which in this case is nonciliated and sometimes transitional. The intervening connective tissue is dense and less vascular than that

shown in case 11, and scattered through it are small groups of alveoli lined by cubical epithelium, while nowhere in the sections can functioning alveoli be found. In addition, adjacent to some of the bronchi can be seen large groups of hypertrophied mucous glands.

A 6 year old girl gave a history of chickenpox and severe pneumonia at the age of 6 months, followed by persistent cough and three further attacks of pneumonia before the age of 3 years, when bronchiectasis was diagnosed (case 13). Death occurred from shock following lobectomy at the age of 6 years, five and one-half years after her first respiratory disease. This lobe showed essentially the same picture as that in case 12 in that it was bound down to the wall of the chest

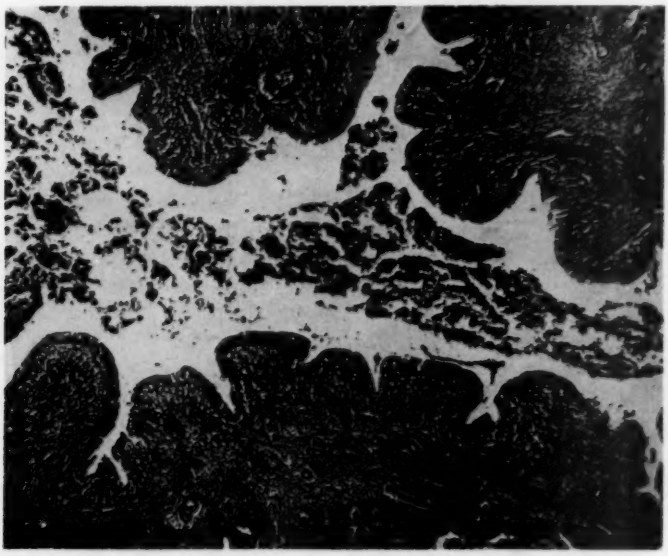

Fig. 13.—Photomicrograph of a longitudinal section of bronchus (case 12) lined by epithelium; × 36.

with old adhesions, and the bronchi showed about the same degree of dilatation, which toward the pleural surface was of the saccular type. They were also lined by redundant mucosa which was thrown into numerous transverse ridges. The parenchyma of the lung had also been largely replaced by fibrous tissue in which could still be seen the remains of a few alveoli lined by cubical epithelium. The main difference between the two specimens lay in the epithelium lining the bronchi; in this instance, it approached more closely the columnar type and in many places was ciliated. This then is the picture of the end-stage of a disease process which had its beginning five and one-half years before in acute pneumonia, and which during those years passed

through the various steps in the stages of destruction and repair that have been shown in the preceding twelve cases.

RELATION OF PULMONARY FIBROSIS TO BRONCHIECTASIS

In tracing the changes in the bronchial walls, brief references have been made to certain alterations in the parenchyma of the lung. In the early cases, these were of the nature of acute interstitial pneumonia. Subsequently proliferation of the connective tissue of the alveolar and interlobular septums resulted in diminution in the size of the alveoli, the lining cells of which often became cubical in shape (fig. 14 *A* and *B*). The ultimate result was one of extensive pulmonary fibrosis, as is well shown in figures 14 *C* and 12.

Faced with such a picture, it is not at all surprising that earlier observers attributed the dilatation of bronchi to traction on the bronchial wall by shrinkage of the intervening fibrous tissue. Among recent writers to express this view are Findlay and Graham,[1b] who concluded their discussion of the etiology of bronchiectasis with the following paragraph: "To our mind the only feasible explanation of the condition is the fibrosis of the lung, as first suggested by Corrigan, with the added influence of pleural adhesions, as first pointed out by Hamilton, since without doubt by providing a fixed point for the contracting fibrous tissue these adhesions increase the traction force of the intrapulmonary fibrosis."

That fibrous tissue contracts is a matter of common knowledge, and that it should contract in the bronchiectatic lung is only to be expected. This contraction takes place not only from side to side, but also parallel to the long axis of the bronchi, so that the lobe is not only narrower but shorter. If this shrinkage takes place in the underlying fibrosing granulation tissue, the mucosa in order to be accommodated to the shortened bronchus must be thrown into folds. Such transverse epithelial folds constitute a striking feature in the chronic case (figs. 12 and 13).

Since fibrosis and contraction occur, the important question, and one over which there has been more or less controversy from the days of Corrigan, is this: Does the traction of the fibroid lung cause dilatation of the bronchi? A review of the histories of the cases here presented reveals the fact that the duration of illness preceding death or operation varied from ten days to five and one-half years. In the first seven cases, the duration ranged from ten days to six weeks, and while all of these showed varying degrees of bronchial dilatation, in some cases marked, yet in no instance at this stage could any pulmonary fibrosis be found, nor were there any fibrous pleural adhesions. Such pulmonary or pleural fibrosis was demonstrable only in the cases

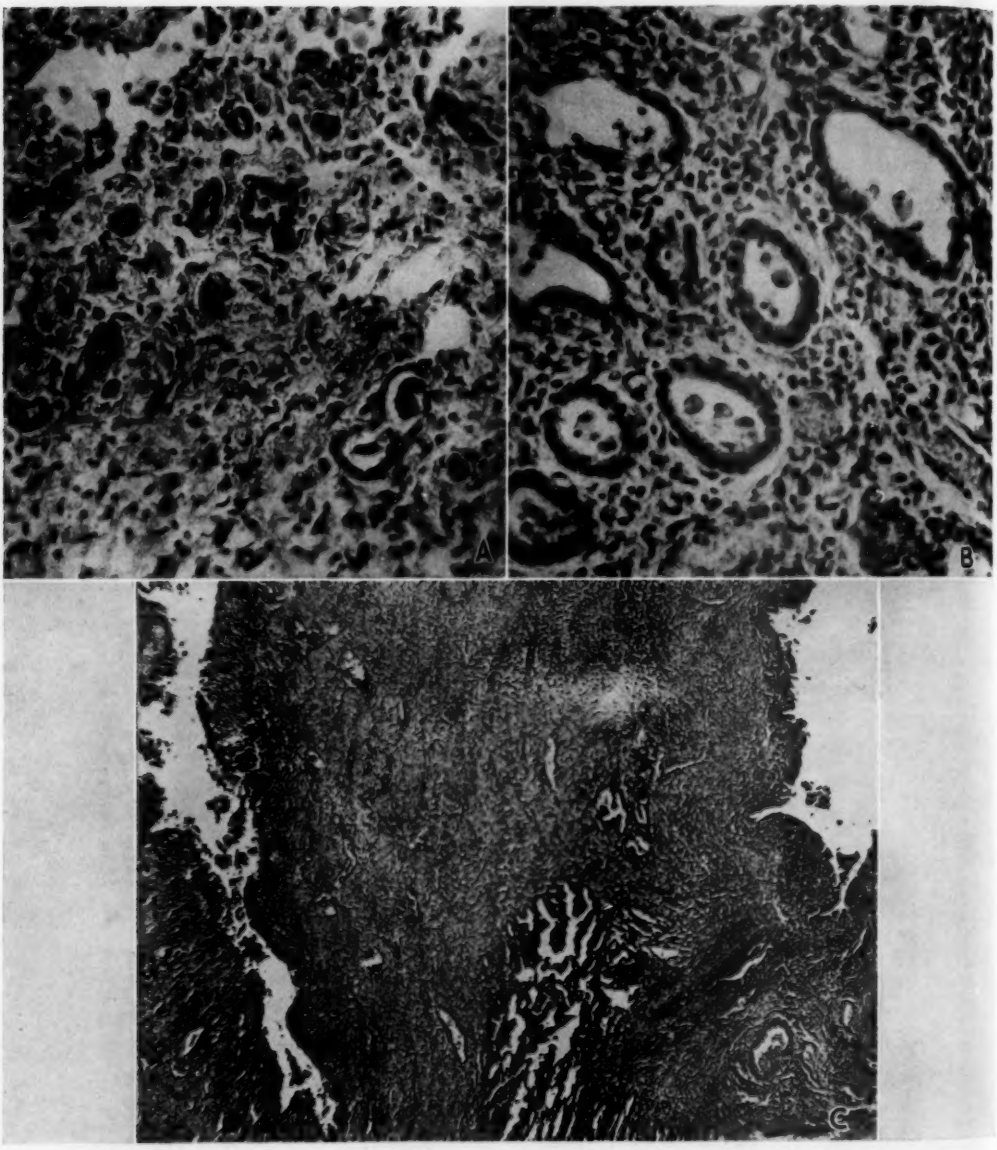

Fig. 14.—*A*, early fibrosis of pulmonary parenchyma with small alveoli lined by cubical epithelium (case 8); × 240. *B*, similar condition (case 10); × 240. *C*, extensive fibrosis in chronic case (case 11); × 36.

of longer standing and was well marked in only the last three cases with symptoms for six and one-half months, almost three years and five and one-half years, respectively. The answer then to the question asked is that bronchial dilatation can and does take place long before the fibroid lung contracts, and the dilatation is, therefore, quite independent of such contraction.

OTHER THEORIES OF ETIOLOGY

Hedblom [7] in a discussion of the pathogenesis of the disease speaks of two fundamental processes entering into the development of acquired bronchiectasis, "namely, infection that weakens the bronchial walls, and mechanical force that produces the dilatation." Of these two processes, he places particular emphasis on the mechanical force, under which he includes atmospheric pressure during inspiration, partial obstruction of a bronchus impeding the exit of air, and pulmonary atelectasis lessening support external to the bronchus. In his opinion, bronchial obstruction is probably the chief cause of atelectasis and atelectasis the cause of bronchial dilatation. In support of this view, he quoted Lichtheim's experiment [8] in which "complete closure of the bronchial lumen leads within 24 hours to atelectasis of the corresponding parenchyma with purulent secretion within the obstructed bronchi. After a few weeks the bronchi near the site of the obstruction dilate. The mechanism is that of atelectasis." In my opinion, the dilatation observed by Lichtheim was the result of an acute bronchitis, as evidenced by the finding of the purulent secretion in the bronchi within twenty-four hours, rather than the result of the associated atelectasis, the destructive effect of such bronchitis being enhanced by lack of drainage.

Other authors, reasoning only from the extreme alterations present in the chronic stage of the disease, have advanced various other theories of the causation, many of the theories having little or no foundation in fact. When, however, the process has been followed from its initial lesion to its chronic stage as shown here, such theories are no longer necessary to explain the picture. As McNeil and his co-workers [1d] so well expressed it: "A bronchiectatic cavity is not a dilated bronchus, but an excavation in the lung substance, starting in a bronchus. . . . It is not necessary in order to explain the existence of the cavities to postulate the operation of any of the factors usually credited with dilating effects. Destruction of tissue and not dilatation is the essence of the process. Nevertheless, those factors may be instrumental in enlarging the cavities after they are formed."

7. Hedblom, C. A.: Surg., Gynec. & Obst. **52**:406, 1931.
8. Lichtheim, L.: Arch. f. exper. Path. u. Pharmakol. **10**:54, 1878-1879.

RELATION OF BRONCHIAL OBSTRUCTION TO BRONCHIECTASIS

While the essential lesion in the production of bronchiectasis is acute ulcerative bronchitis, there is another very important factor which must not be overlooked. This factor is that of mechanical obstruction. Failure to take this into consideration has led various authors to believe that bronchitis, per se, has little to do with the cause of bronchiectasis. To quote Findlay and Graham [1b]: "Surely if uncomplicated bronchitis played any prominent part in causing the condition, bronchiectasis would be a much more common finding than it is." The question then may well be asked, If bronchiectasis has its origin in bronchopneumonia, bronchitis or some other type of acute respiratory disease, why do these respiratory diseases so frequently resolve without the development of bronchiectatic lesions? It may be said that the explanation lies in the type or virulence of the causative organism or organisms. While this view may possess an element of truth, it by no means embraces the common factor which determines whether or not a given case of pneumonia or bronchitis will resolve or progress to bronchiectasis. The determining factor in the great majority of instances is, I believe, mechanical obstruction.

One of the essential principles in the treatment of any acute suppurative process is free drainage, and any interference with such drainage tends to accentuate the destructive process in the inflammatory zone. The importance, therefore, of mechanical obstruction at once becomes apparent. This is perhaps nowhere more evident than in acute ulcerative appendicitis; frequently an appendix with a constricted lumen at its base or somewhere in its proximal half will show immediately beyond the constriction, either with or without the presence of an enterolith, an acute ulcerative process with the lumen distended with foul-smelling pus. If this exudate cannot be discharged into the cecum and operation is delayed, destruction of the wall may proceed to perforation. Similarly obstruction plays an equally important part in ulcerative bronchitis. The obstructing agents may vary widely in their nature, position and distribution, but the effects are essentially the same. In the series of cases reported here, perhaps the most obvious instance of obstruction was the plugging of a bronchus by a tooth (case 3). At autopsy, the tooth was found embedded in edematous bronchial mucosa and beyond it the destructive process had advanced in some areas to well marked fusiform dilatation of the passages (fig. 2 *A* and *B*), while elsewhere it had gone on to extensive pulmonary gangrene. Though it is true that the organisms in this case, namely fusospirochetal bacteria, are known to produce a greater degree of destruction than do pyogenic cocci, nevertheless the interference with free drainage further accentuated the destructive process. Additional evidence of the

importance of obstruction is found in a case [9] in which bronchiectasis followed aspiration of a tack (fig. 15). Foreign bodies constitute a menace not only by producing obstruction, but also by carrying into the lung large numbers of bacteria; particularly is this true of teeth, which are usually heavily infected. Another example of obstruction is found in case 6, in which a large caseous gland pressed against the bronchus, causing partial obliteration of the lumen. Here again the bronchiectasis developed in the portion of the lung corresponding to the obstructed bronchus (fig. 5). While the primary pulmonary lesion was tuberculous in origin, the secondary ulcerative process was caused by pyogenic cocci, the activities of which were enhanced by inadequate drainage; this part of the disease process was, therefore, nontuber-

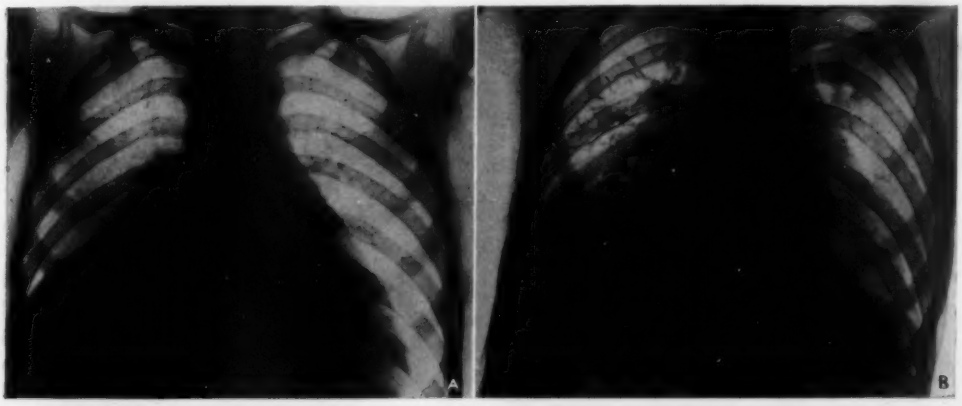

Fig. 15.—*A*, x-ray picture of chest (case 14), showing a foreign body in a bronchus, about one year after the "swallowing" of a tack; *B*, x-ray picture following removal of the foreign body and introduction of iodized poppy seed oil 40 per cent.

culous. Other cases of bronchiectasis developing as the result of pressure on a bronchus from without by a new growth have been observed, but in my series there is no example of such.

Of perhaps equal importance with but less spectacular than foreign bodies, caseous glands and tumors are the obstructions caused by inflammatory exudates. In some instances, the bronchial mucosa becomes so infiltrated with cells and so edematous as to encroach greatly on its own lumen, interfering materially with free drainage. As the disease progresses and the ciliated epithelial cells are destroyed, the beneficial action of the cilia is lost and a vicious circle is established. The nature of the exudate is also important; if thick, tenacious exudate remains

9. A synopsis of this case is given at the end of table 2.

in the bronchus of a pneumonic lung, the destructive process in the bronchial wall is augmented. This is well shown in figure 4 *B*, picturing a bronchus in which organization of the bronchial exudate is already taking place four and one-half weeks after the onset of symptoms. Such organization can occur only in a stagnant exudate. This case is of particular interest because the symptoms were largely those of respiratory obstruction, and foreign body was suspected but not demonstrated. Then, because of associated laryngitis, tracheotomy was performed to relieve the obstruction; the latter, however, proved at autopsy to be not in the larger air passages, but in the smaller bronchi, and took the form of stagnant exudate with beginning organization.

These cases demonstrate that the one most important factor favoring ulceration is inadequate drainage whether resulting from foreign bodies, caseous glands, swollen mucosa or inspissated exudate; and as these conditions do not obtain in the great majority of cases of pneumonia or bronchitis, resolution takes place in this majority without the development of bronchiectasis.

RELATION OF PULMONARY ABSCESS AND GANGRENE TO BRONCHIECTASIS

It might be argued that some of the acute cases in my series are not cases of bronchiectasis but examples rather of acute pulmonary abscess or gangrene, i. e., the first three cases reported. In case 1, it is true, some of the abscesses were obviously of embolic origin and not in direct communication with the bronchi. In addition to the embolic lesions, however, there was also severe ulcerative bronchitis, and some of these ulcerated bronchi opened out into definite abscess cavities. This is also true of case 2, while in case 3 there were large patches of gangrene.

Had these patients not succumbed to the disease, it is possible that the cavities in the process of healing subsequently would have been surrounded by granulation tissue and later relined with epithelium, presenting the picture seen in the last five cases. In this connection, the statement of McNeil and his co-workers [1d] will bear repetition: *"Destruction of tissue and not dilatation is the essence of the process."* The degree of destruction may vary from superficial ulceration to extensive abscess formation or gangrene. Kline [1e] held a similar view, and in discussing the pathology of bronchiectasis he stated: "Not infrequently there is total destruction of a portion of the bronchus and lung, with cavity formation, especially in the saccular type."

By whatever term, then, these acute conditions are known, whether acute bronchiectasis, pulmonary abscess, gangrene or suppuration of

the lung,[10] if the process has resulted in destruction of bronchial walls, the lungs are essentially bronchiectatic, and if recovery takes place, the end-result in the majority of these cases will be one of chronic bronchiectasis. I say "in the majority of cases" because it should be borne in mind that in certain cases of suppuration of the lung recovery may take place without such permanently dilated bronchi. Such healing, with diminution in the size of the bronchi, depends, I believe, on early diagnosis and institution of adequate drainage before the enlarged bronchi become relined by epithelium. This drainage not only tends to prevent further destruction of tissue, but favors healing during the period in which the walls are lined by granulation tissue. When once a new epithelium has been laid down, permanent dilatation is the result. Jackson[10] emphasizes the importance of drainage as follows: ". . . . the fundamental factor in all pulmonary pathology is impaired defensive power of the lung due to impaired drainage and aeration. By bronchoscopic drainage we take the load off the cilia and restore spontaneous drainage. With the restoration of aeration and spontaneous drainage we re-establish the defensive powers of the lung."

INADEQUATE DRAINAGE IN CHRONIC CASES

Clinically, inadequate drainage is one of the outstanding features of a well established case of untreated bronchiectasis. A study of such a case (case 12) reveals the cause. In the normal lung the bronchial walls are provided with a definite system of muscle fibers.[11] In case 12, these muscle fibers have been destroyed, so that the peristaltoid movement of the bronchi, so important in the removal of secretion,[12] no longer obtains. Closely coupled with this is the relative absence of elastic fibers. Moreover, by the replacement of the destroyed epithelium with a modified nonciliated type, as is so frequently the case in the bronchiectatic lung, another extremely important agent in the removal of secretion has disappeared. A third factor is the saccular or fusiform type of dilatation, in this instance chiefly the former. Even if muscle and elastic fibers were still present and the epithelium ciliated, the emptying of such cavities as are shown in figure 12, with the patient in the erect position, would seem well nigh impossible. Little wonder then that with the loss of these structures and their respective physiologic functions the cavity remains veritably a septic tank. A fourth factor comes into play as the disease progresses, and fibrosis becomes more marked. As the fibrous tissue contracts, the lung becomes shortened and the

10. Jackson, Chevalier: New England J. Med. **199**:759, 1928.
11. Macklin, C. C.: Physiol. Rev. **9**:1, 1929.
12. Macklin, C. C.: Arch. Surg. **19**:1212, 1929

bronchial mucosa is thrown into numerous folds to accommodate it to the shortened space (figs. 12 and 13). Such transverse folds of redundant mucosa must still further add to the difficulties of drainage.

To sum up, then, not only has the bronchus because of the destruction of much of its muscle and elastic tissue and ciliated epithelium lost its ability to discharge the accumulating secretions, but it is faced with the added burden of emptying large cavities through a channel across which have been erected many obstructions in the form of transverse ridges of mucous membrane.

RESTORATION OF STRUCTURE AND FUNCTION

What possibilities of recovery does a chronic bronchiectatic lung possess? Before attempting an answer, permit me to draw attention again to the salient features of such a lung. Briefly these are: widely dilated bronchi, with walls composed largely of connective tissue lined by modified epithelium; partial to complete absence of muscle and elastic fibers in the bronchial walls; abundant bronchial secretion swarming with bacteria; fibrosis of adjacent parenchyma to such an extent as almost to obliterate the alveoli, and contraction of the affected lobe. Such a lung not only is incapable of performing its function, but is also a source of bacterial infection to the accessory nasal sinuses. Restoration of function to such an extensively damaged lung does not seem possible; but even if function cannot be restored, can healing be promoted to such an extent as to remove the foci of infection and thus improve the patient's general health?

To accomplish this it would seem necessary to obliterate completely the useless bronchi and so convert the lung into a solid fibrous mass. Partial obliteration must result in the walling off of epithelium-lined pockets into which secretion will still pour, thus providing a medium for bacterial growth. These bronchi may be compared to sinuses draining infected wounds or abscesses in deep tissues, and if healing is to occur, the same process of repair must take place as obtains in the healing of a sinus elsewhere; namely, granulation tissue must grow gradually from the depths of the sinus toward the surface, leaving no pockets of pus or foreign matter behind. The bronchiectatic lung possesses a multitude of such sinuses, many of which have saccular or fusiform dilatations, lined by epithelium which in itself is a barrier to healing by granulation tissue. To obliterate all these sinuses with their innumerable ramifications would first require the destruction of all this lining epithelium and the adjacent mucous glands, a task which is nothing short of impossible. Removal of the whole lobe, therefore, would seem to hold forth the only hope of permanent cure in this type of case.

BACTERIOLOGY

Various bacteria have been credited with the production of this disease, chief among which have been perhaps streptococci [13] and the fusospirochetal group either alone or in combination with other organisms. Smith [14] was able to show that what he describes as primary bronchiectasis could be produced in rabbits by intratracheal injection of pus containing spirochetes, fusiform bacilli, vibrios and cocci. He concluded that "the fuso-spirochetal group of organisms is probably the cause of primary bronchiectasis."

In my opinion, the cause of bronchiectasis, whether primary or secondary, cannot be attributed to any one organism or group of organisms, any more than can all cases of pneumonia and bronchitis be traced to a common cause. Greey [15] concluded his bacteriologic study of nine lobectomized lungs with this significant statement: "The variety of micro-organisms recovered suggests that no specific type plays an

TABLE 1.—*Micro-Organisms Found in Twenty-Six Cases of Bronchiectasis in Children*

Bacillus influenzae	10	M. catarrhalis	3
Hemolytic streptococci	10	Spirochetes	2
Nonhemolytic streptococci	8	Unidentified organisms	11
Strep. viridans	6		
Pneumococci	6	Staphylococcus alone	3
Fusiform bacilli	5	Pneumococcus alone	2
Staph. aureus	3	Strep. viridans alone	1

Four cases showed 2 organisms only; in the remaining cases, usually more than 3 of the organisms listed were present in various combinations

etiologic rôle, but that many bacteria are capable of producing bronchial damage sufficient to favor dilatation." In a series of cases investigated in this hospital, various bacteria were found alone or in combination, as shown in table 1.

Many of the bacterial investigations reported by other authors, as well as those of my more chronic cases, have been carried out on expectorated sputum, material aspirated from the bronchi or that obtained from surgical specimens. Such bacteria recovered from the chronic case are no indication of those originally responsible for the lesion. It is a matter of common knowledge that the discharge from chronic otorrhea yields on culture a great variety of organisms in large numbers, including diphtheroid bacilli and Bacillus proteus, while the original cultures at the onset of the acute otitis media were pure cultures of hemolytic streptococci or pneumococci. Frequently neither

13. Thorpe, E. S., Jr.: Am. J. M. Sc. **177**:759, 1929.
14. Smith, D. T.: Arch. Surg. **21**:1173, 1930.
15. Greey, P. H.: J. Infect. Dis. **50**:203, 1932.

of the latter can be found after long-standing suppuration, for they have been long since overgrown by secondary invaders, many of which are relatively nonpathogenic. The bacteriology, therefore, of bronchiectasis is not that of the chronic bronchiectatic lung, but of the bronchopneumonia or other acute respiratory disease which marked the onset of symptoms.

TABLE 2.—*Résumé of Cases*

Case	Reference	Sex	Age	Duration of Symptoms	History
1	A/215/31	M	4 yr.	10 days	Acute bronchitis and purulent bronchopneumonia (Staph. aureus) of 10 days' duration, complicating typhoid fever
2	A/132/25	M	6 wk.	10 days	Acute bronchitis and purulent bronchopneumonia
3	A/218/29	F	6 yr.	3 wk.	Acute bronchiectasis and pulmonary gangrene following aspiration of tooth during epileptic seizure (Vincent's organisms)
4	A/169/27	M	6 mo.	3½ wk.	Head-colds since birth; cough 3½ weeks; acute bronchiectasis and bronchopneumonia
5	A/130/31	M	5 yr.	4½ wk.	Whooping cough and "cold in chest" 4½ weeks; short, shallow breathing 3 weeks
6	A/109/29	F	2½ yr.	5 wk.?	Pulmonary tuberculosis; compression of bronchus by caseous glands
7	A/219/24	F	4 yr.	6 wk.	Whooping cough 6 weeks; pneumonia at least 1 month (B. influenzae and pneumococci)
8	A/ 63/26	M	19 mo.	6½ wk.	Cough and otitis 6½ weeks; pneumonia at least 1 month
9	A/124/31	F	11 mo.	4½ mo.?	Cough and head-cold 4½ months; bronchitis, bronchiectasis and bronchopneumonia of uncertain duration
10	A/ 23/32	F	6½ mo.	5 mo.?	Cough and failure to gain weight 5 months; acutely ill with fever and rapid, shallow and difficult breathing 12 days
11	A/115/25	M	8 mo.	6½ mo.	"Rattle in throat" 6½ months; severe cough 4 months
12	S/ 84/32	F	3 yr.	2½ yr.	Pneumonia almost 3 years before lobectomy; symptoms continuous
13	S/166/32	F	6 yr.	5½ yr.	Chickenpox and severe pneumonia at age of 6 months, followed by persistent cough; three further attacks of pneumonia before age of 3 years, when bronchiectasis was diagnosed; death from shock following lobectomy at 6 years of age
14	Clinical case	M	9 yr.	3 mo.	"Swallowing" of tack 12 months before admission to hospital; no symptoms for 9 months, then loss of appetite and of weight, and frequent headaches, followed in 2 months by pain in the chest and cough; no sputum; foreign body removed about a year after aspiration; bronchiectasis demonstrated 3 weeks after its removal

RELATION OF BRONCHIECTASIS TO DISEASE OF THE UPPER RESPIRATORY TRACT

A number of authors [16] are of the opinion that upper respiratory disease plays a large part in the production of bronchiectasis. There is a strong possibility that sinusitis, otitis media, etc., may develop more often in patients suffering from bronchiectasis because of the danger of secondary infection of these regions from the enormous numbers of bacteria coughed up into the mouth from the bronchi. On the other hand, since bronchiectasis so frequently follows bronchopneumonia, and as the latter is more apt to occur in a person with accessory nasal sinus

16. Adam, J.: J. Laryng. & Otol. **40**:172, 1925. Ochsner, A.: South. M. J. **25**:149, 1932.

disease than in one with a healthy upper respiratory tract, the possibility of accessory sinus disease being indirectly responsible for bronchiectasis cannot be ignored entirely. While certain evidence, therefore, may be produced on either side, I prefer to adopt the view expressed by Lemon,[17] who stated: "Bronchiectasis may or may not develop in consequence, and alternately sinusitis and so forth, may or may not develop subsequent to the establishment of bronchiectatic disease. That they frequently are related is dependent on the establishment of a vicious circle. . . . It is better to consider the diseases as fundamentally infectious and related, but not necessarily in ordered sequence."

SUMMARY

A pathologic study of thirteen cases of bronchiectasis is presented here. In eleven of these the lungs were obtained at autopsy; in the other two cases, pathologic studies were conducted on lobectomized lobes. The lobes obtained at operation were from cases of almost three years' and five and one-half years' duration, respectively. The other cases had a history of symptoms attributable to the respiratory system lasting from ten days to six and one-half months. One case followed aspiration of a tooth, and one, compression of a bronchus by caseous tuberculous glands. The ages of the patients at the time of death or of operation ranged from 6 weeks to 6 years.

A brief report is added of a clinical case in which bronchiectasis followed the aspiration of a tack.

CONCLUSIONS

Bronchiectasis has its origin in some type of acute respiratory disease. The essential lesion is an acute ulcerative bronchitis with destruction of epithelium, muscle and elastic fibers of the bronchial wall, frequently with extension of the destructive process into the surrounding parenchyma of the lung. This destructive process is favored by mechanical obstruction interfering with free drainage of the bronchus. The obstructing agent may be a foreign body, caseous mediastinal glands, a neoplasm, swollen bronchial mucosa or inspissated exudate. As the process of destruction proceeds, the bronchial lumen becomes surrounded by a wall of highly vascular granulation tissue in which muscle and elastic tissue elements are usually absent. This granulation tissue then becomes relined by epithelium, which is frequently of a modified type, and as the former becomes fibrosed, a simultaneous fibrosis takes place in the adjacent parenchyma of the lung.

17. Lemon, W. S.: M. Clin. North America **10**:531, 1926.

The appearance of the bronchi in the early stages of bronchiectasis before relining with epithelium takes place is such as to suggest that healing at this stage with actual diminution in size of the bronchi may be promoted by bronchoscopic drainage. When once the bronchi become relined with epithelium, such healing is no longer possible.

While fibrosis of the lung commonly accompanies bronchiectasis, nevertheless, bronchial dilatation can and does occur long before the newly formed fibrous tissue has begun to contract; the dilatation, therefore, cannot be the result of contraction of the fibrous tissue.

When a whole lobe is involved in the advanced chronic stage of bronchiectasis, it has absolutely no value from the standpoint of function. It may, moreover, be the source of infection of the accessory nasal sinuses, to the inflammation of which it may contribute. Drainage from such a lobe is retarded by partial or complete loss of muscle and elastic tissue in the bronchial walls and of cilia on the lining epithelium, and by the presence of transverse folds of mucosa. The healing of such a lobe by conversion into a solid fibrous mass is rendered impossible by the presence of innumerable epithelium-lined cavities and dilated bronchi.

The bacteriology of bronchiectasis is the bacteriology not of the chronic bronchiectatic lung, but of the bronchopneumonia or other acute respiratory disease which marked the onset of symptoms. While both pyogenic cocci and fusospirochetal organisms may be found in early cases, the most destructive lesions are produced by the latter group.

AN ATTEMPT TO TRANSMIT POLIOMYELITIS TO SPLENECTOMIZED GUINEA-PIGS

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There have been many attempts to discover some animal other than the monkey which is suitable for experimental studies on poliomyelitis. If this could be done, advances might be made in knowledge of poliomyelitis comparable to those concerning yellow fever which followed the demonstration by Theiler [1] that white mice can be used as well as monkeys for experimental purposes.

Harmon, Shaughnessy and Gordon [2] have reported the negative results of repeated efforts to transmit poliomyelitis to animals of many kinds. I have proceeded in a slightly different way, for I splenectomized the animals before inoculation. It was thought that removal of the spleen might lower their resistance so that the virus might "take" in animals in which it would not ordinarily do so. There is a considerable amount of evidence that resistance to other infective agents can be decreased in this way. Thus Bradford and Plimmer [3] concluded that splenectomized animals died more rapidly from an infection with Trypanosoma brucei than animals that possessed spleens. Removal of the spleen has been found to modify the production of specific hemolysins and hemagglutinins (Motohashi,[4] Bieling and Isaacs,[5] and Siegmund [6]). According to Neufeld and Meyer,[7] mice could no longer be immunized against pneumococci after blockading and splenectomy. Davis [8] reported that splenectomy aggravated the course of experimental piroplasmosis in cats. Kligler [9] found that splenectomized rats show a complete absence of resistance to trypanosome infec-

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1. Theiler, M.: Ann. Trop. Med. **24**:249, 1930.
2. Harmon, P. H.; Shaughnessy, H. J., and Gordon, F. B.: J. Prev. Med. **4**:59, 1930; **4**:89, 1930.
3. Bradford, J. R., and Plimmer, H. G.: Quart. J. Micr. Sc. **45**:449, 1902.
4. Motohashi, S.: J. M. Research **43**:473, 1922.
5. Bieling, R., and Isaacs, G.: Ztschr. f. d. ges. exper. Med. **28**:180, 1922.
6. Siegmund, H.: Klin. Wchnschr. **1**:2566, 1922.
7. Neufeld, F., and Meyer, H.: Ztschr. f. Hyg. u. Infektionskr. **103**:595, 1925.
8. Davis, L. J.: Ann. Trop. Med **25**:79, 1931.
9. Kligler, I. J.: Ann. Trop. Med. **23**:315, 1929.

tion when the inoculation is given intraperitoneally. But the most significant observations are those of de Kock and Quinlan,[10] who discovered that after splenectomy, oxen and sheep, which were carriers of anaplasmosis but devoid of symptoms, regularly exhibited marked intensification of the disease reaction; their blood swarmed with parasites, and all the classic symptoms appeared.

The transmission of poliomyelitic virus to splenectomized guinea-pigs was attempted because of their convenient size and the ease with which they tolerate splenectomy. It was also felt to be desirable to check the claims of Neustaedter [11] and Picard [12] that they had successfully transmitted the virus in guinea-pigs and Creutzfelt's [13] claim that he had found lesions typical of poliomyelitis in Picard's guinea-pigs. Another advantage of using guinea-pigs is the fact that in contrast to rabbits (Oliver [14]) and mice (Cowdry and Nicholson [15]) they have not thus far been found to exhibit spontaneous encephalitic lesions.

Though I have not been successful in transmitting the virus to these animals I wish to report my experiments very briefly. The guinea-pigs selected weighed between 150 and 250 Gm. A postoperative period of from two to five days was allowed before inoculation. The virus was a 5 per cent suspension in physiologic solution of sodium chloride of the brain and cord of a monkey that showed symptoms of the disease. Its potency was proved by injection into other monkeys. All the inoculated guinea-pigs were given intracerebrally 0.5 cc., intraperitoneally 5 cc. and subcutaneously 1 cc. of virus.

In the first group of experiments, ten splenectomized and two unsplenectomized animals were inoculated with virus. There were two sets of controls; one, consisting of two splenectomized and two unsplenectomized guinea-pigs, received in the same way an emulsion of normal monkey's brain; while the other, consisting of one splenectomized and one unsplenectomized animal, was not inoculated and was merely held for observation. The results are given in table 1.

On the assumption that repeated passage might result in transmission, a second group of experiments was undertaken. Three splenectomized and two unsplenectomized guinea-pigs were inoculated in the manner described, while one splenectomized animal and one unsplenectomized were inoculated with normal monkey's brain. They were put to death on the fourth day. Their brains were removed

10. de Kock, G., and Quinlan, J.: Eleventh and Twelfth Reports of the Director of Veterinary Education and Research, Union of South Africa, p. 369.

11. Neustaedter, M.: J. A. M. A. **50**:982, 1913.

12. Picard, H.: Ztschr. f. Hyg. u. Infektionskr. **105**:307, 1926.

13. Creutzfelt, H. G.: Ztschr. f. Hyg. u. Infektionskr. **105**:342, 1926.

14. Oliver, J.: J. Infect. Dis. **30**:91, 1922.

15. Cowdry, E. V., and Nicholson, F. M.: J. Exper. Med. **40**:51, 1924.

aseptically, and a 5 per cent emulsion was made which in turn was inoculated into a second series of guinea-pigs. After the lapse of three days these were killed, and a similar transfer was made to a third series

TABLE 1.—*Results of Direct Inoculation of Splenectomized Guinea-Pigs with Poliomyelitic Virus*

Experiment	Physical Condition	Pathologic Observation
	A. Inoculation with Monkey Virus *	
110†	Animal dead 3 days after inoculation; no involvement of nervous system	Hemorrhagic pneumonia; lymphoid hyperplasia; central nervous system normal
111†	Marked meningeal reaction and convulsions 6 days after inoculation, followed by prostration and death	Bronchopneumonia; small abscess of left lung; lymphoid hyperplasia of cervical, submental and mesenteric nodes; meninges edematous, congested; brain and cord congested; no characteristic pathologic changes
112†	Weakness and sluggishness 10 days after inoculation, lasting 3 to 4 days; then animal became alert and active; put to death	Lymphoid hyperplasia; no changes in central nervous system
114†	Died 14 days after inoculation; no involvement of nervous system	Lungs congested; mesenteric lymph nodes enlarged; brain and cord normal
115†	Died 14 days after inoculation; no involvement of nervous system	Bronchopneumonia; nervous system normal
116†	Died 14 days after inoculation; no involvement of nervous system	Bronchopneumonia; general lymph node hyperplasia; nervous system normal
118†	Died 12 days after inoculation; no involvement of nervous system	Edema of right lung; nervous system normal
119†	Died 14 days after inoculation; no involvement of nervous system	Brain somewhat infected; meninges edematous; mesenteric lymph nodes enlarged
124†	No effect observed	
125†	Flaccid paralysis of both hind legs on third day following inoculation; temperature, 97 F.; killed for passage virus; emulsion of brain and cord inoculated into three splenectomized guinea-pigs	Lumbar cord: marked congestion, multiple pinpoint hemorrhages, interstitial edema, no typical perivascular infiltration or obvious changes of anterior horn cells. Lymphoid hyperplasia
131	No effect observed; put to death after 5 weeks	No obvious pathologic changes
136	No effect observed; put to death after 5 weeks	No obvious pathologic changes
	B. Inoculation with Normal Monkey Brain *	
120†	No effect observed; put to death after 5 weeks	Mesenteric lymph nodes slightly enlarged; no other pathologic changes
121†	No effect observed; put to death after 5 weeks	No obvious pathologic changes
126	No effect observed; put to death after 5 weeks	No gross pathologic changes
127	No effect observed; put to death after 5 weeks	No gross pathologic changes
	C. No Inoculation	
123†	No effect observed.....	Slight lymphoid hyperplasia
130	No effect observed.....	No gross pathologic changes

* All inoculations were made as follows: intraperitoneally, 5 cc.; intracerebrally, 0.5 cc.; subcutaneously, 1 cc.
† Splenectomized.

of guinea-pigs. This third set was kept for a period of five weeks and killed for examination. A similar experiment was conducted using two splenectomized and one unsplenectomized animal for initial inoculation, but, in addition to the brain emulsions of these animals being transferred serially, potent monkey virus was added (replacing one-half the original dose) with each transfer inoculation. The results are presented in table 2.

COMMENT

Of the ten splenectomized guinea-pigs inoculated with monkey poliomyelitic virus, only one animal presented symptoms suggestive of an involvement of the spinal cord. Guinea-pig 125 on the third day

TABLE 2.—*Results of an Attempt to Establish Poliomyelitis by Serial Transfers in Splenectomized Guinea-Pigs*

Experiment, Initial Inoculation (1st Day)	First Transfer (4th Day)	Second Transfer (7th Day)	Physical Conditions Observed	Pathologic Observations
A. Inoculation with Monkey Virus Passed Through 2 Guinea-Pigs*				
143†	148†	182†	No effect observed; died after 12 days	Bronchopneumonia; brain and cord normal
	149†			
144†	150†	183†	No effect observed; put to death after 5 weeks	No gross changes
	151†	184†	Died after 4 days	Bronchopneumonia; striking lymphoid hyperplasia
145†	152†	185†	No effect observed; put to death	Enlarged lymph nodes
	153†	186†	No effect observed; put to death	Enlarged lymph nodes
Pooled virus using central nervous systems of guinea-pigs 143, 144, 145	154†	187†	No effect observed; died after 14 days	Congestion of lungs; lymphatic hyperplasia; no gross changes in nervous system
	155†	188†		
146 (control)	158	189	No effect observed; put to death	No gross pathologic changes
147 (control)	159	190	No effect observed; died after 3 weeks	Bronchopneumonia
B. Inoculation with Passage Virus Plus Monkey Virus*				
143†	156†	181†	Died after 4 days	Lymphatic enlargement; edema of lungs
144†	157†	192†		
Pooled virus from guinea-pigs 143, 144	142†	193†		
146	160	194	No effect observed; put to death	No gross pathologic changes
C. Inoculation with Normal Monkey Brain*				
161†	195†	196†	No effect observed; put to death	No gross pathologic changes
198	199	201	No effect observed; put to death	No gross pathologic changes

* All inoculations were made as follows: intraperitoneally, 5 cc.; intracerebrally, 0.5 cc.; subcutaneously, 1 cc.
† Splenectomized.

following inoculation with potent monkey virus suddenly developed flaccid paralysis of both hind extremities; but there was no obvious general reaction. The animal ate well, seemed alert and did not have fever. The brain and cord taken from it were ground into an emulsion and transferred to three splenectomized guinea-pigs. No effects were observed in these animals. Microscopic examination of the lumbar cord of guinea-pig 125 showed numerous pinpoint hemorrhages with some

edema, but no characteristic perivascular or interstitial lymphocytic infiltration, destruction of anterior horn cells or neuronophagia. Römer [16] described a disease like poliomyelitis which arose spontaneously in guinea-pigs. Monkeys were not, however, susceptible to the disease, and other characteristics implied that it was a virus disease distinct from poliomyelitis.

Guinea-pig 111 showed meningo-encephalitis on the sixth day following inoculation, with opisthotonos and convulsions, followed by prostration and death. The meninges were edematous and congested, as was also the surface of the brain and cord. Microscopic examination of the cord showed no evidence of the characteristic myelitis.

That splenectomy alters the general resistance of the animal was well borne out by the experiments. The daily records of temperature and clinical symptoms and signs showed that invariably the splenectomized guinea-pigs reacted more severely to the procedures employed. Not one unsplenectomized animal died during the five week period. They were killed for examination.

Another noticeable feature was that the splenectomized animals inoculated with poliomyelitic virus reacted more severely than those given injections of an emulsion of normal monkey's brain. No deaths occurred before five weeks in animals inoculated with pure brain emulsion. A rise in temperature and some degree of sluggishness usually followed inoculation with the virus; these symptoms were more outspoken than with the pure monkey brain. Animals 125 and 111, which showed signs of an involvement of the nervous system were inoculated with virus.

Perhaps the most outstanding feature at postmortem examination was lymphoid hyperplasia. The mesenteric lymph nodes, the supraclavicular group, the submental and the inguinal glands were often enlarged to a striking degree. That lymphoid hyperplasia is often found following splenectomy as a compensatory mechanism is well known and naturally must first be considered. This hyperplasia, however, is rarely acute, and examination of splenectomized controls failed to show any special enlargement of the lymph nodes. A second consideration is the fact that the introduction of any inoculum into the peritoneal cavity or subcutaneous tissues usually calls forth some lymphatic activity regardless of the nature of the material used. This fact was confirmed by the finding of some degree of hyperplasia of the mesenteric nodes in guinea-pigs inoculated with normal monkey brain.

And thirdly, the lymphatic response to the virus of poliomyelitis has long been recognized. Only recently Burrows [17] reviewed this phase

16. Römer, P. H.: Deutsche med. Wchnschr. **37**:1209, 1911.
17. Burrows, M. T.: Arch. Int. Med. **48**:33, 1931.

of the disease, and concluded that the most common feature of poliomyelitis is "hyperplasia of some or all of the lymphatic structures of the organism." In the fatal cases he noted that the mesenteric lymph nodes were generally more hyperplastic than the other glands, which, however, were generally enlarged. This author even goes so far as to state that "This disease (poliomyelitis) is not a primary disease of the central nervous system; it is a disease of the lymphatic system of the body."

The increase in temperature, general malaise, sluggishness and lymphoid hyperplasia indicate some reaction on the part of the splenectomized guinea-pig to the virus; but the more classic picture—that of an involvement of the nervous system—was absent.

CONCLUSIONS

Splenectomized guinea-pigs do not acquire the nerve lesions characteristic of poliomyelitis following inoculation with potent monkey virus, either in direct or in passage experiments. Splenectomized guinea-pigs do show a decrease in resistance to such inoculation, which produces, in many, a condition characterized by fever, general sluggishness and lymphoid hyperplasia, with death often occurring within fourteen days.

Laboratory Methods and Technical Notes

WEISS COAGULOFLOCCULATION TEST OF MALIGNANCY

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The obvious value of a serologic method for the detection of malignancy has led to many attempts to devise such a procedure, among the more recent of which is the reaction proposed by Weiss.[1]

The mechanism of the reaction is not discussed by Weiss, but apparently it depends on the colloidal instability of the serum and is thus similar to the precipitation reactions occurring in syphilis. Like these, also, it is simple in technic, requiring a mixture of serum and antigen in regulated proportions followed by dilution with an electrolyte.

TECHNIC OF TEST

The following materials are necessary for the conduct of the test:

Glassware.—For the measurement of serum and antigen 1 cc. and 0.2 cc. pipets are needed, as well as test tubes such as are used for the Wassermann test and a small flask. It is important that all glassware be thoroughly clean and preferably prepared as for the conduct of colloidal gold tests.

Antigen.—One hundred grams of beef heart muscle, freed from fat and finely ground, is extracted with 1,000 cc. of 95 per cent alcohol for three days at 37 C. After standing over night at room temperature, the extract is filtered and stored in dark, rubber-stoppered bottles.

Titration of Antigen.—In each of two rows of eight tubes place the following doses of antigen: 0.12, 0.14, 0.16, 0.18, 0.20, 0.22, 0.24 and 0.26 cc. To each tube in the front row add 0.6 cc. of serum from a patient known to have a malignant growth, diluted as described under the test proper; and to each tube of the back row add 0.6 cc. of syphilitic serum similarly diluted.

Shake thoroughly, incubate five minutes at from 54 to 55 C. in a water bath, and add to each tube slowly 2.5 cc. of saturated solution of sodium chloride.

In accordance with the resultant turbidity and flocculation, three "zones" may be distinguished.

The "lower nonspecific zone" is that occurring with the smaller doses of antigen; it is recognized by the occurrence of turbidity in both rows of tubes. With the larger doses of antigen, flocculation occurs in both rows, constituting the "upper nonspecific zone," while in between these zones certain tubes will be seen in which only turbidity occurs in the syphilitic serum, whereas in the row containing serum from the patient with a malignant growth more or less pronounced coagula float on the surface of the saline solution with smaller flocculi suspended throughout the solution. This is the "specific zone."

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1. Weiss, E.: Arch. Path. **13**:106, 1932.

The dose of antigen for the test is the largest amount which, by titration, produces only turbidity with syphilitic serum and definite coaguloflocculation with malignant serum.

Salt Solution.—Sodium chloride, chemically pure, 40 Gm., is added to distilled water, 130 cc.

Serum for the Test.—Serum for the test should be freshly collected, thoroughly cleared by centrifugation and not inactivated. Chylous or hemolytic serum or that showing bacterial contamination is unsatisfactory.

Preliminary Dilution of Serum.—The degree of dilution of the serum is dependent on the hemoglobin content, which must be determined by a relatively accurate method, the Tallqvist scale not being satisfactory. The formula for the determination is: $\frac{Hb\% + 10}{20}$ = dilution. Example: If hemoglobin is 70 per cent, $\frac{70 + 10}{20} = \frac{80}{20} = 4$. The dilution of the serum should be 1:4. When the hemoglobin is 40 per cent or less, the serum is diluted 1:2.5.

All dilutions of the serum are made with distilled water.

The Test.—Two rows of tubes are set up in a rack, the front row containing the unknown serum to be tested (in tube 1), and also malignant, syphilitic, icteric and anemic serums as controls, all being diluted as described. The last tube of the first row contains no serum and serves as the antigenic control. The tubes in the back row are the serum controls.

The dose of antigen is now added to all tubes of the *first* row, and a corresponding volume of *distilled water* to the back row. The rack is then shaken and placed in a water bath at from 54 to 55 C. for five minutes; it is then removed and 2.5 cc. of the saturated salt solution is slowly added to each tube and the reaction read.

Reading of the Test.—The malignant control tube should show the characteristic coaguloflocculation; all the other controls, turbidity only.

The unknown serums are compared with the malignant control, those showing a similar reaction being recorded as strongly positive. A distinct flocculation with absence of a surface layer of coagulated serum is read as weakly positive, while uniform turbidity or doubtful flocculation is recorded as negative.

Weiss emphasized the necessity of syphilitic, icteric and anemic controls, the inference being that under these conditions fallacious reactions may occur.

The following sources of error must be avoided: (1) the use of hemolytic, contaminated, inactivated or chylous serum; (2) incorrect dilution; (3) use of some diluent other than distilled water; (4) inaccurate titration of antigen; (5) failure to mix antigen and serum thoroughly; (6) incubation at improper temperature (too high or too low); (7) failure to use saturated saline solution for dilution after incubation; (8) incubation for less or more than five minutes, and (9) agitation of tubes after the addition of saline solution, which makes the reading difficult, if not impossible.

With this procedure, Weiss reported negative reactions in 98.05 per cent of nonmalignant serums from a variety of conditions, and strongly positive reactions in 79.33 per cent of one hundred and seventy-nine malignant serums, weakly positive reactions in 6.15 per cent and negative reactions in 14.52 per cent.

In view of the simplicity of the test and the results reported by Weiss, the procedure was carried out in these laboratories on serum obtained mainly from the gynecologic services of Dr. W. P. Conaway and Dr. W. E. Darnall, whose cooperation is hereby acknowledged.

The antigen was prepared from polytropic beef heart powder used for the preparation of antigens for precipitation tests and complement-fixation tests in syphilis (Difco).

All hemoglobin determinations, on which the serum dilutions depended, were made by the method described by Haden,[2] which is regarded as one of the most accurate at present available.

As icteric and anemic serums are not always readily obtainable, as recommended by Weiss for controls, the following plan was adopted and carried out for all patients tested.

As already stated, the icterus index was determined in all cases. count) was made for each patient, which furnished not only the percentage of the hemoglobin for determination of the serum dilution, but also evidence for or against the presence of anemia to be taken into consideration in the later reading of the test.

Positive syphilitic serum was always available for a control, but a complement-fixation (Kolmer) test and a precipitation (Kline) test were done for each patient. The possible influence of icterus was checked by the determination of the icterus index for each patient.

With these exceptions, the procedure described by Weiss was followed in detail.

RESULTS

The true character of the results obtained may best be demonstrated by separation of the cases into groups either in accordance with the diagnosis or in accordance with the various characteristics of the serums.

There were but eight serums in the series giving positive reactions to the complement-fixation test (one to five tube fixation in Kolmer's quantitative test) and positive precipitation (Kline) reactions. Of these, three gave strongly positive, and two, doubtful Weiss reactions, only one, however, being from a patient with a malignant growth (carcinoma of the cervix). While the number is small, the results suggest that the Weiss reaction cannot be safely interpreted in syphilitic serum, and that a syphilitic control is essential.

As already stated, the icterus index was determined in all cases. Clinical jaundice with an index of 21.5 was encountered in only one case, a case of pernicious vomiting, while in nine cases the readings fell within the "zone of latent jaundice" without, however, any apparent influence on the incidence of positive Weiss reactions.

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2. Haden, R. L.: J. Lab. & Clin. Med. **16**:68, 1930.

The effect of anemia was definitely apparent in the series studied. Anemia, of course, is a relative term, but for the purpose of this study all cases in which there was an erythrocyte count of less than 4,000,000 per cubic millimeter and a hemoglobin content of less than 11.5 Gm. (74 per cent per hundred cubic centimeters) were included in this group. Of sixty-seven such cases, twenty-two gave definitely positive, and five, doubtful Weiss reaction. In only ten of these cases was a malignant growth present.

While the influence of the other conditions present, besides the anemia, cannot be disregarded, it was clearly evident that the more marked the anemia, the greater the incidence of positive Weiss reactions, so that it may be concluded that anemia is not without influence on the production of the reaction. To what extent this influence is exerted it is difficult to determine, for in many of these cases inflammatory processes and benign tumors (fibroma uteri) were present, both of which seem to exert an appreciable influence on the Weiss reaction.

Of thirty-eight serums from patients presenting only inflammatory processes (salpingitis, peritonitis, appendicitis, etc.), thirteen gave strongly positive Weiss reactions. Of this group, only fifteen were also included in the group classified as anemic.

Any procedure to be of value in the diagnosis of a malignant condition must be relatively free from positive reactions in the presence of benign tumors, but of twenty serums from patients presenting fibroma uteri, five gave strongly positive, and one, a doubtful Weiss reaction.

In the series were sixteen serums from patients with carcinoma of various sites, as follows: cervix, ten; sigmoid, two; rectum, one; breast, one; urethra, one, and fundus uteri, one. Definitely positive Weiss reactions were encountered in only six of these, the remainder being consistently negative, some on several tests.

While Weiss, in his communication, does not advance any theory as to the underlying mechanism of the coagulofloccculation reaction, it seems probable that it can be correlated with the varying degrees of colloidal instability of the serum which have recently attracted attention.

Among such reactions are those to the precipitation tests in syphilis and perhaps—although here, too, the mechanism is in dispute—those to the sedimentation test.

As the sedimentation test is practically a routine procedure in the gynecologic services, an opportunity is afforded to compare the results of the Weiss test with varying types of sedimentation reactions.

If both reactions have as a common factor changes in the colloidal stability of the serum, the incidence of positive Weiss reactions should be in proportion to the rapidity of sedimentation or, in other words, to the degree of activity indicated by the results of the sedimentation test.

That such a proportionate relation seems to exist is shown by the data following:

Of thirty-two serums in cases in which the results of the sedimentation test indicated an absence of activity of the lesions, six, or 18 per cent, gave positive Weiss reactions, and twenty-six, or 80 per cent, negative reactions.

Of sixteen serums in cases in which the results of the sedimentation test showed slight activity, two, or 12 per cent, gave positive Weiss reactions and fourteen, or 87 per cent, negative reactions. Of thirty-five serums in moderately active cases, fourteen, or 40 per cent, yielded positive, and eighteen, or 51 per cent, negative Weiss reactions; while of nineteen in cases showing marked activity, six, or 31 per cent, gave positive, while thirteen, or 71 per cent, gave negative Weiss reactions.

It is interesting to note that some degree of parallelism between the results of the Weiss and sedimentation tests is indirectly evidenced by the data presented concerning the cases grouped as inflammatory and those presenting benign tumors, in both of which conditions increased sedimentation reactions commonly occur.

CONCLUSIONS

While the series tested is not extensive, the evidence secured is fairly definite, and suggests that the Weiss coaguloflocculation test is nonspecific; that the positive reactions occur with definite frequency in cases of anemia and syphilis and in the presence of benign tumors; that in malignant conditions the reactions are neither uniform nor constant and are related, apparently, more to the degree of destruction of tissue or to that of activity of growth than to the presence of malignant growth per se, and that because of the relatively frequent nonspecific reactions and the relatively frequent occurrence of negative reactions in cases of malignant growth, a diagnosis of malignancy cannot be based with safety on the results of the Weiss test.

General Review

CERTAIN PHASES OF THE PROBLEM OF ROCKY MOUNTAIN SPOTTED FEVER

A SUMMARY OF PRESENT INFORMATION

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Only a few years ago Rocky Mountain spotted fever was thought to be a relatively obscure disease confined to a limited portion of the northern Rocky Mountain region. Today it is recognized as an infection of nation-wide concern and of world-wide interest.

It is nearly thirty-three years since this typhus-like disease was described by Maxey as a clinical entity. During this period, the recognized endemic area in the West has been extended consistently year by year until it now reaches well toward the Pacific Coast, northward into Canada, and southward into the states bordering Mexico, while to the eastward the recent reported occurrence of an apparently identical infection in a considerable number of southern, central and far eastern states leaves one to wonder if there may not be discontinuous occurrence from the Pacific to the Atlantic.

It is but a short time, too, since Dermacentor andersoni Stiles, a wood tick apparently limited to the Rocky Mountains and adjacent areas, was thought to be the only transmitting agent. Now another wood tick that occurs in greater or less abundance in most other sections of the United States is also a demonstrated vector to man, while of five more species, two appear to be definitely concerned in the maintenance of the infection in nature and the other three to be potential if not actual carriers to man.

The annual expenditure of funds for research and control has increased from a few hundred dollars made available in 1902 by the Montana State Board of Health for the initial studies of Wilson and Chowning to over $100,000. The greater portion of this amount is being expended by the United States Public Health Service and the balance by the State of Montana. Montana alone, since 1902, has expended well over $300,000.

The early research laboratories of Ricketts and others in the Bitterroot valley were housed in tents and log cabins. My own first animal laboratory at Victor in 1920 was an old woodshed in the rear of my residence. However, as the increasing importance of Rocky Mountain spotted fever and other tick-borne diseases has become more and more apparent, research facilities have been gradually improved. Four years ago the State of Montana completed at Hamilton, in the Bitterroot valley, a modern laboratory at a cost of $65,000. This laboratory was built solely for work on ticks and Rocky Mountain spotted fever and was especially designed to limit, as far as possible, the extreme hazards that have always attended research in this disease. This laboratory has recently been taken over by the Public Health Service, and a $75,000 addition is soon to be built. Even with the increased space, however, we shall still be hampered for the adequate accommodation of the varied activities which it is necessary to carry on incident to the investigation being made. The staff at the present time consists of twenty-four full time and nine part time members.

Scientific interest has also expanded. For many years the disease was considered a curiosity of little interest except to a limited number of practicing physicians. Outside the investigators that have been associated directly or indirectly with the State of Montana or the Public Health Service, it attracted scant attention. However, the recent extensive additions to the areas in which Rocky Mountain spotted fever is known to be endemic, the knowledge that D. andersoni is an agent in the transmission or causation of three and probably four disease entities of man (Rocky Mountain spotted fever, tularemia, tick paralysis and Colorado tick fever), and the fact that other species of ticks are known to be potential carriers of some, at least, of these diseases have created a widening interest and a resultant increase in the number of institutions in the United States in which research is being conducted. Furthermore, there has been a growing interest in Rocky Mountain spotted fever in foreign countries, and strains of the virus for research purposes are being maintained in a considerable number of laboratories at various widely separated points of the globe. The latter interest arises from the fact that Rocky Mountain spotted fever belongs to the group of typhus-like diseases, concerning the variety, distribution and importance of which knowledge is continually increasing.

In the pages which follow, I shall deal mainly with certain special phases of the problem of Rocky Mountain spotted fever. These are, nevertheless, an essential part of the knowledge of this disease. However, much that is of historical interest must be omitted, and if therefore I may seem to fail to accord due recognition to some of the valuable studies which have been made, it will not have been because of lack of appreciation of their merit.

I. TICKS IN RELATION TO THE TRANSMISSION OF ROCKY MOUNTAIN SPOTTED FEVER AND THEIR DISTRIBUTION WITHIN THE UNITED STATES

The experimental demonstration of the transmission of Rocky Mountain spotted fever by the common wood tick of the Rocky Mountain region, D. andersoni, was made independently by Ricketts and by King in 1906, and in 1907 the former demonstrated the occurrence of naturally infected ticks of this species in the Bitterroot valley of western Montana. These data, together with the epidemiologic findings, were conclusive evidence of the part which this tick plays in the causation of human infection. Later Ricketts demonstrated that virus acquired by either of the immature stages of this wood tick was transmitted to the adults of that generation, and that from at least a certain proportion of infected females the infection was transmitted with the egg of their progeny. These studies constituted the first demonstration of a tick-borne disease of man in this country.

D. andersoni occurs throughout the Rocky Mountain region and adjacent areas. To the west, it extends well to the Cascade range in Washington and Oregon, and is present in the northeastern part of California, and south along the east slope of the Sierras. To the east, it extends into the southwestern corner of North Dakota and probably occurs in the Black Hills country of western South Dakota. There is no evidence of its occurrence in Nebraska, and in Colorado it perhaps does not extend far beyond the eastern limit of the Rocky Mountain system. In the south, it occurs in at least the northern portions of New Mexico and Arizona. On the north, it extends a considerable distance into the Canadian province of Britsh Columbia and is present in at least the southern portions of the provinces of Alberta and Saskatchewan.

Among the later experiments of Ricketts were tests to determine whether or not Rocky Mountain spotted fever was transmissible by other species of ticks. The results were published after his death in 1911 by Maver. It was found that infection could be recovered (1) from nymphs of Dermacentor variabilis Say, the American dog tick, which had received infection as larvae, (2) from adults of Dermacentor parumapterus-marginatus Banks, the rabbit tick which had been infected as nymphs, and (3) from both nymphs and adults of Amblyomma americanum (L.), the Lone Star tick, which had been infected as larvae. These experimental results were for many years deemed of no practical interest, since D. variabilis and A. americanum did not occur at all, and D. marginatus only slightly, within the limits of the Rocky Mountain spotted fever endemic area as then known. Furthermore, D. marginatus was known not to bite man.

The second tick demonstrated to be a natural carrier of Rocky Mountain spotted fever virus was the rabbit tick, Haemaphysalis leporis-palustris Pack. This I established in 1923. The studies on the rabbit tick were the outgrowth of field observations made in eastern Montana in 1916 and 1917 which had suggested that under the epizootilogic conditions concerned, some agent other than D. andersoni was likely involved in the natural maintenance of the virus. Evidence suggested the rabbit tick, but opportunity to carry out the necessary studies did not occur until several years later. In 1921, experimental transmission was demonstrated, and infected rabbit ticks were recovered from nature. Subsequently, it was also shown that transmission of the virus from generation to generation occurs as in D. andersoni.

While the rabbit tick does not bite man and is only of indirect concern in human infection, it nevertheless is probably very important in the complex of factors concerned in the maintenance of the virus in nature. As concerns this tick, there are two points of considerable interest: first, that the type of Rocky Mountain spotted fever virus carried by this tick is rarely capable of producing other than extremely mild infections; and second, that the rabbit tick is the only known carrier of the virus of Rocky Mountain spotted fever which occurs in all sections of the United States where this infection is now known to be endemic. It is present in greater or less abundance throughout the United States.

The third tick indicated as a natural carrier, and the second which evidence points to as concerned in the infection of man, was D. variabilis, the American dog tick, the same tick with which Ricketts experimented prior to 1911. The complicity of this tick was suggested only last year by the work of Rumreich, Dyer and Badger (1931) of the National Institute of Health, and was the outgrowth of their joint studies of endemic typhus in the East and South. Suffice it for the purpose of this paper to state that they found (1) that cases of typhus-like infection originating in rural sections of certain of the eastern states which had theretofore been diagnosed as endemic typhus were in reality indistinguishable immunologically and clinically from Rocky Mountain spotted fever, and (2) that the epidemiologic evidence indicated D. variabilis as the carrier. Their subsequent laboratory studies have demonstrated that eastern strains of the virus of Rocky Mountain spotted fever acquired by larval ticks of this species were later transmissible by the nymphs and adults of the same generation. Thus far, infected D. variabilis has not been definitely recovered from nature, although in 1931 R. G. Green, of the University of Minnesota Medical School, and I secured results in tests of this tick collected in Minnesota

which were suggestive of the presence of a very mild type of the virus of Rocky Mountain spotted fever.

D. variabilis occurs over the greater portion of the eastern United States from the Atlantic seaboard westward to, and in some sections beyond, the eastern limit of the occurrence of D. andersoni. There are scattered reports of its occurrence in certain of the Rocky Mountain states, and in one section of eastern Montana its range overlaps that of D. andersoni by at least 150 miles. It again becomes abundant in parts of California and extends northward into southern Oregon.

Studies of the virus-carrying propensities of ticks other than D. andersoni were begun at the Hamilton laboratory in 1929. They were undertaken because the constant outpushing of the known affected area of the Rocky Mountains—the only section of the United States in which spotted fever was then thought to be endemic—had carried both its eastern and western limits beyond the known range of the Rocky Mountain wood tick, so that it seemed extremely probable that other ticks, the ranges of which overlapped that of D. andersoni, might have become involved. D. variabilis on the east and the west, and Dermacentor occidentalis (Neum), on the southwest, were the species particularly in mind at that time. Experimentally, both species have been found to be transmitters of Rocky Mountain strains of the virus. In the case of D. variabilis, stage to stage transmission as reported by Maver and by Dyer, Rumreich and Badger has been confirmed, and, in addition, hereditary transmission has been shown. With D. occidentalis the infection has been carried within the limits of a generation, material not being available for more extended tests. The range of D. variabilis has previously been noted. D. occidentalis occurs throughout a large portion of California and in southern and southwestern Oregon, and it is doubtless but a question of time until this tick will be implicated as an agent of infection in man.

In 1931, stimulated by the discovery of infection of the type of Rocky Mountain spotted fever in eastern states, still further tests were made with Rhipicephalus sanguineus Latr., the brown dog tick, and A. americanum, the Lone Star tick. The former is an occasional, the latter a frequent, parasite of man. Both occur in the southeastern portion of the country, the former being most prevalent near the sea coast, particularly of the Gulf States, though it also occurs in considerable numbers on islands off the southeastern coast of Massachusetts and also has been reported from Kansas, Ohio and New York.

With Rhipicephalus sanguineus my associates and I have again been able to demonstrate transmission from larval to adult tick and from female to offspring. Although there is no evidence at present to incriminate this tick as a carrier of typhus-like infections in the United

States, the recent evidence that it is involved in the transmission of eruptive fever in countries of the Mediterranean littoral point to it as a tick to be watched, not only for this disease, but also for Rocky Mountain spotted fever.

Our experiments with A. americanum have only recently been started, but results already secured, when combined with those of the early tests of Ricketts, indicate in this tick again transmission of the virus both from stage to stage and from generation to generation. With its wide host relationships and its frequent occurrence on man, it seems likely that this species, too, may soon be proved an agent of human infection. In this connection, it is of interest that Spencer (1926) and Glasser (1930) reported separately a case of unidentified typhus-like infection in a woman residing in Norfolk, Va., who had been bitten by a tick, presumably A. americanum, which came from a calf hide shipped from either North Carolina or some point in Virginia. In 1931, Dr. Noxon Toomey, of Palmyra, Mo., reported a fatal case of what was apparently Rocky Mountain spotted fever, supposedly caused by this tick, and in connection with several reputed cases occurring near Shreveport, La., during the past year, this tick was the only species found on the premises concerned by representatives of the Federal Bureau of Entomology. Ticks of the species A. americanum thus collected were submitted to me for test by F. C. Bishopp of the Bureau of Entomology, and one of these ticks induced a reaction in guinea-pigs which experience thus far has led us to consider indicative of the presence of the virus of Rocky Mountain spotted fever.

In summary, there are, within the limits of the United States, two wood ticks, D. andersoni and D. variabilis, which are known to be transmitters of the virus of Rocky Mountain spotted fever to man; three others, D. occidentalis on the west coast and A. americanum and R. sanguineus in the southeastern United States, which are unquestionably potential, and in the cases of the first two, perhaps actual carriers to man; and still two others, H. leporis-palustris and D. marginatus, which transmit infection in nature, but which are thereby indirect agents of human infection. That still other species will be found to be actual or potential carriers is extremely probable.

One or more of these ticks proved to be actual or potential carriers of Rocky Mountain spotted fever occur in each of the forty-eight states of this country.

II. THE VIRUS OF ROCKY MOUNTAIN SPOTTED FEVER

Dermacentroxenus rickettsii is the generally accepted etiologic agent of Rocky Mountain spotted fever. This rickettsia was first definitely associated with the disease by Wolbach (1916) and was described by

him in 1919. Kuczynski and Brandt (1926, 1927) are the only investigators who claim successful cultivation in artificial mediums, but thus far their results have not been confirmed. Several rickettsia-like organisms have been isolated from infected D. andersoni, but none have proved pathogenic. Neither have they immunized against known strains of virus nor have they been agglutinated by the serums of persons ill with Rocky Mountain spotted fever or convalescent from it. In our somewhat limited experiments and those of Spencer (1932) no relationship between Bacillus proteus X organisms and the virus, as claimed by some European workers, has been found.

The virus may be studied as it occurs in the blood or other tissues of experimental animals and of man, or in the tissues of ticks. Virus from these three sources will hereafter be referred to as "blood virus" or "passage virus," "tissue virus" and "tick virus," respectively, and unless otherwise specified, all references to tick virus refer to the virus of D. andersoni.

Strains of blood virus are best maintained in guinea-pigs. The simplest procedure to this end, when dealing with highly virulent strains, is the intraperitoneal transfer of blood from the heart, taken preferably about the fourth day of fever. Highly fatal strains can usually be maintained indefinitely with minor fluctuations of virulence, if intercurrent infections can be avoided. Very mild strains, however, are more difficult to establish. Tick virus will always be available if strains of infected ticks are maintained as rearing stock, the successive stages of the ticks being permitted to engorge as need demands.

It is necessary to utilize the reactions of laboratory animals for the qualitative and quantitative studies of the types of virus. For this purpose the male guinea-pig is the most suitable animal, because of cost, availability and the diagnostic reactions provoked. The highly susceptible monkey and less susceptible rabbit are valuable for special purposes.

BLOOD VIRUS

Infectiousness.—The properties of blood virus have been studied particularly by Ricketts, Wolbach (1919), Connor (1924) and Spencer and Parker. The infectiousness of whole blood virus from man or animals varies greatly. The minimum amount of blood required to produce infection in a guinea-pig may be as small as 0.001 cc. or as great as several cubic centimeters. In general, blood is more infectious when taken about the middle of the course of infection. Rarely do injections of whole blood virus produce unapparent infections. In my experience, whole blood virus is the most infectious, defibrinated blood virus the next, and serum virus the least. The red and white cells are also infectious.

Resistance and Viability.—At room temperature, citrated or defibrinated blood virus seldom remains infectious for as long as eight days. It is killed at temperatures of from 45 to 56 C. in from five to thirty minutes, depending on the technic employed (Ricketts, 1907; Wolbach, 1919). It does not resist desiccation (Ricketts, 1907).

According to King (1930), guinea-pig whole blood virus, when frozen in sealed tubes, remains infectious in 1 cc. units up to forty-eight days, and in 7.5 cc. units up to ninety-five days. Subsequent tests, even in amounts of 15 cc., are noninfective.

I have found that at from 1 to 3 C. blood virus containing one-fifth part of 2 per cent sodium citrate solution and tested at two day intervals will retain its infectiousness in 1 cc. doses for twenty-four days with but slight loss of virulence, defibrinated blood virus for twenty-two days but with marked loss of virulence after fifteen days, and serum virus for only six days. Citrated whole blood virus, when covered with a layer of liquid petrolatum and tested at seven day intervals, showed decreasing virulence after twenty-one days, but was still infectious at forty-two days. These periods are considerably longer than those recorded for earlier studies (Ricketts, 1907; Wolbach, 1919).

Filtration.—All attempts to pass serum virus through Berkefeld filters have failed.

Distribution of Virus in the Blood.—Ricketts (1907) concluded from the results of qualitative tests of the virus of Rocky Mountain spotted fever in the blood stream of monkeys that there is a general plasmatic infection, and also emphasized the "tenacity with which virus associates itself with the blood corpuscles," from which it could not be separated by repeated washings. Spencer and Parker (1926) obtained similar results. They found that red and white cells washed twelve times by centrifugation at 1,200 revolutions per minute for three minutes were still infectious. They further showed that when infected cell-free guinea-pig serum was mixed with an equal volume of a suspension of washed *normal* red cells, the latter became infectious, and that 0.1 cc. quantities were still infectious after ten washings. A similar result was obtained with white cells. No affinity for the platelets was shown.

Centrifugation.—The virus is not readily brought down by centrifugation. Ricketts (1907) found that centrifugation of infected monkey serum did not free the overlying portion of virus. Similarly, Spencer and Parker (1926) found the overlying portion of guinea-pig serum virus still infectious after centrifugation for fifteen minutes at 8,800 revolutions per minute.

Occurrence of Rickettsiae in the Blood.—The high degree of infectiousness of blood virus seems incompatible with the very small number

of rickettsiae which can usually be demonstrated in smear preparations. Ricketts (1909) stated that they could be found in any preparation of infectious blood after not more than a half hour's search. According to Wolbach (1919), the demonstration of the organism in the circulating blood is extremely difficult. Connor (1924) was able to demonstrate a few apparent rickettsiae in smears of the residue after centrifugation for six hours at 2,000 revolutions per minute. Spencer and Parker (1926) found only a few scattering rickettsia-like organisms in the sediment after the high speed centrifugation mentioned in the foregoing paragraph, and none in the overlying serum.

Properties of Killed or Attenuated Serum Virus.—Serum virus, whether killed or attenuated by heat or by chemicals, is without immunizing value. This has been amply attested by the studies of Ricketts, Wolbach, Noguchi, Connor, Spencer and Parker.

TISSUE VIRUS

The essential lesions of Rocky Mountain spotted fever originate in the vascular system. These lesions are responsible for the rash, edema, hemorrhages and necrosis of the infection as it occurs in man and laboratory animals. Their distribution agrees with the occurrence of the virus in tissues which is described by Wolbach (1916) as follows:

> The organisms are found in apparently uninjured endothelium of normal vessels, in areas of proliferated endothelium of the intima of vessels, in hyaline necrosed intima of more advanced lesions, in apparently normal and necrosed smooth muscle fibers of vessels with lesions and in endothelial cells in the perivascular zones of proliferation. They occasionally occur within the endothelial cells in dilated lymphatics. They may also be found between the cells and vessels showing lesions and in fat tissue and edematous connective tissue. The largest masses are seen in smooth muscle cells of affected arteries and veins and occasionally they occur in enormous numbers in such cells.

The properties of tissue virus have been but little studied and then only as regards infectiousness, viability and immunity-provoking power when attenuated or killed.

Breinl (1926) found that the brains and testicles of exsanguinated guinea-pigs contained 100,000 infectious doses of virus. Spencer and Parker found the testicles and spleens of guinea-pigs and rabbits to contain usually 1,000 infectious doses per gram. In isolated instances, guinea-pig spleen was found infectious in doses of 0.00006 Gm., and rabbit testicle in doses of 0.00003 Gm.

It appears probable that this high degree of infectiousness is due to intracellular virus of the organized tissues and not to remnants of blood virus. However, it is not clear whether it is qualitative or quantitative. Breinl and also Spencer have observed rickettsiae in enormous numbers in testicular tissue. On the other hand, in highly infectious

brain tissue, Reimann (1928) was able to demonstrate rickettsiae in only one of eight brains sectioned, and then in one focus only.

Observations on the viability of the tissue virus have been made as follows:

Wolbach (1919) found that at from 7 to 10 C. the virus in guinea-pig testes, spleen, liver and kidney, when preserved in 25 and 50 per cent glycerin, was infectious at the end of five days but not in a month, no intermediate tests being made.

Spencer and Parker (1924) showed that the virus in guinea-pig tissues was viable after more than ten months in 100 per cent glycerin at —10 C. without apparent loss of virulence. Testicular tissue was more favorable for preservation than either spleen or liver. The brain was not used.

King (1929), using guinea-pig tissues preserved in 50 and 100 per cent glycerin at from —1 to —2 C., found 100 per cent viability in twenty days, but only 14 per cent in tests made in from forty to sixty days. He considered brain the best tissue for the preservation of virus. In frozen brain tissue used in later tests, King was able to demonstrate viable virus after three hundred and twenty-one days.

In the experiments of Spencer and Parker and of King, the results varied considerably with individual specimens of the different tissues used.

Connor (1924) demonstrated that preserved tissue virus will frequently immunize. His most constant results were secured with guinea-pig testicles that had been frozen or had been dried in a vacuum at —7 C. Dried splenic tissue proved negative. Spencer and Parker secured immunity with 1 Gm. of phenolized emulsion of the aforementioned rabbit testicle which was infectious to 0.00003 Gm., and in one instance with testicular tissue which was infectious only to 0.001 Gm. Immunity was occasionally secured with similar phenolized emulsions of guinea-pig testicles and spleens. However, most tests of both rabbit and guinea-pig testicles and spleens were negative.

In several instances I have found that emulsified but otherwise untreated guinea-pig splenic tissue, removed post mortem and injected into guinea-pigs intraperitoneally, resulted in immunity without apparent evidence of infection.

Since all evidence is opposed to the production of immunity by killed or attenuated blood virus, it is perhaps reasonable to assume that an immunity following the injection of treated tissues is due to altered tissue virus and not to any property of blood virus remaining in the tissues used. Tissue virus, therefore, probably differs from blood virus in that, when attenuated by suitable methods, it sometimes provokes immunizing reactions.

TICK VIRUS

Tick virus as it occurs in tick tissue offers perhaps the most potentially profitable field for research of the various phases of the problem of Rocky Mountain spotted fever. Such studies have already led to the production of a vaccine and to some knowledge of the properties and behavior of tick virus, a broad understanding of which is desirable for the intelligent interpretation, not only of experimental results, but also of epizootilogic data. How essential this knowledge really is and how the lack of it could and has easily led to erroneous deductions may be appreciated by the additions made by recent research to knowledge of the range of virulence of virus in ticks, and of the means by which the presence of infection in ticks can be demonstrated. For example, it was formerly supposed that if a tick was infected, the virus would always provoke in guinea-pigs the characteristic scrotal lesions of a clinically recognizable infection, and that if a tick feeding on a guinea-pig failed to produce these symptoms, it had been definitely demonstrated that it was an uninfected tick. From studies of tick virus it is known now (1) that the virus may exist in ticks in a phase of such low virulence that it produces only unapparent infections which are not clinically recognizable, and (2) that if a tick fails to infect by feeding, additional tests that may require a total of from twenty to thirty days for completion are necessary in order that one may be even reasonably certain that the tick does not contain virus, and that apparently negative results must even then be accepted with caution. These points will be more fully discussed.

The properties of tick virus as such were but little studied before 1921. The more recent Public Health Service investigations beginning that year, on the other hand, have been largely concerned therewith, and the following more significant findings have been selected from the great mass of accumulated data. These studies were made by R. R. Spencer and myself during the period from 1922 to 1928, and since then by G. E. Davis, C. B. Philip and myself. Findings referable to other research workers are so indicated.

In the discussion that follows, the terms "infectiousness" and "virulence" as applied to tick virus mean the ability of the virus to produce specifically recognizable or demonstrable infections and the degree of severity of such infections, respectively.

Stage-to-Stage and "Hereditary" Transmission of the Virus.—Ricketts (1906-1909) found that when virus from an infected host is ingested by larval or nymphal ticks, it is passed on to adults of the generation concerned, and that some infected females at least will pass it on through their eggs to the larvae of the next generation.

These observations have been repeatedly verified by subsequent investigators.

Transition of Ingested Blood Virus to Tick Virus and Invasion of Tick Tissues.—Experimental studies have indicated that when virus is ingested by a tick, it loses the qualities of blood virus and takes on those of tick virus, and that this is followed by a period during which it invades the tick tissues, infection not being transmissible until this invasion has proceeded to such a point that the virus has become established in the salivary glands. Spencer and Parker (1930) have termed this a "period of invasion." It is best demonstrated in adult ticks. When normal adults are first fed on an infected host just long enough to insure ingestion of virus and then transferred directly to a normal host, the tick feeding thus being interrupted but essentially continuous, our tests have shown a period of from nine to twelve days between the ingestion and the transmission of the virus. The same ticks which are unable to transmit infection by biting during this period nevertheless cause infection if emulsified and injected into susceptible animals.

Functional Changes of Tick Virus.—However, except under accidental or experimental conditions, infection is not thus transmitted by the same stage of the tick that acquires it, but instead by the next and subsequent stages. This is because larval, nymphal and female ticks usually complete their engorgement during a single uninterrupted feeding on a single host, and since the successive stages engorge in succeeding years, there is a period of from six months to a year or sometimes longer between the acquisition of virus by one stage of the tick and its possible transmission by the next, or between its transmission by successive stages in strains of ticks in which infection is already established. There has been a corresponding functional adaptation of the virus. When ingested, it takes on the qualities of tick virus, as noted, and tissue invasion begins. At this stage the virus is highly virulent and produces typical infections in laboratory animals. However, after the ingestion of fresh blood has ceased, the engorged tick having detached itself from its host, the virus gradually decreases in virulence in most ticks until it finally becomes so low grade that it is able to induce only unapparent infections, and our more recent observations suggest that sometimes the virus may even lose entirely its infectious quality and persist in a nonsymptom-producing, nonimmunizing phase which cannot be specifically demonstrated. It is in these low grade phases that the winter is passed. Not infrequently, though not consistently, these changes of infectiousness and virulence are accompanied by marked morphologic changes.

Therefore, when the infected ticks emerge from hibernation in the spring, the virus, when demonstrable, is of a degree of virulence not higher than one capable of producing unapparent infections. If, however, such ticks are subjected to incubation or allowed to ingest blood, the virus usually regains its ability to produce frank infections. This transition from a low grade hibernating phase to a highly virulent, symptom-producing phase following incubation or feeding we have termed "reactivation."

It is therefore apparent that after the virus is established in a given strain of ticks, its life consists of short periods of high virulence coincident with and immediately following the engorgement of each successive stage, and alternating much prolonged periods of greatly reduced functional activity during which it is seldom capable of inducing more than symptomless infections.

Relation of Demonstrable Rickettsiae to the Infectiousness of Tick Virus.—The relation of demonstrable rickettsiae in ticks to their infectiousness is an interesting question which in our opinion has not yet been elucidated. Rickettsiae are usually, though not consistently, relatively scarce in hibernating ticks. On the other hand, in infected ticks in which opportunity has been permitted for the "reactivation" of the virus by incubation or by the ingestion of fresh blood, there is usually an accompanying remarkable increase in the number of demonstrable rickettsiae and in the virulence of the tick virus.

If a considerable number of adult ticks infected in an antecedent stage and of identical subsequent history are tested by permitting "reactivation" of the virus by feeding, and then each tick is injected into a guinea-pig after making smears of the several tissues, it is found that the majority show a large number of rickettsiae and contain highly virulent virus. However, there are often two smaller groups, in one of which the ticks are highly virulent but the smears show few rickettsiae, while in the other the ticks are noninfectious yet rickettsiae are abundant.

In one series of tests, a comparison was made of the relative number of rickettsiae and the virulence of tick virus in two groups of adult ticks, one but recently infected as adults, the other infected as larvae and in which the virus had been resident for a long time. The former showed small numbers of rickettsiae, not generally distributed, and were infectious for guinea-pigs to a ten-thousandth part of a tick. The latter showed large numbers of generally distributed rickettsiae but were not infectious to more than a five-thousandth part of a tick. Furthermore, the latter group before feeding showed more numerous rickettsiae than did the former after infection had been acquired, and yet the former contained the larger number of minimum infectious doses per tick.

Owing to these observations and others of similar nature, we have reached the tentative conclusion that there is a stage of the virus, which for some reason cannot be seen with the ordinary microscope. The existence of such a stage is also suggested by some of the studies of blood and tissue virus recorded in foregoing paragraphs, as, for example, the relatively small number of demonstrable rickettsiae in blood that is highly infectious and the failure of Reimann (1928) to demonstrate rickettsiae in all but one of eight sectioned, highly infectious guinea-pig brains.

Range of Virulence.—In any individual tick infected with a highly virulent strain of Rocky Mountain spotted fever, the limits of demonstrable virulence of the resultant tick virus are, at one extreme, symptomless, unapparent but immunizing infections, and, at the other, infections causing 100 per cent mortality. Most of the latter extremely virulent infections provoke characteristically high febrile reactions and produce in male guinea-pigs the scrotal lesions typical of Rocky Mountain spotted fever. In some instances, however, there is such exaggerated toxicity that guinea-pigs die afebrile on the third, fourth or fifth day after inoculation.

If ticks are infected with strains of a lower maximum degree of virulence, such as prevail in most areas where Rocky Mountain spotted fever is endemic, then the demonstrable limits of the range of virulence are not so far apart. The lower limit is the same, but the maximum is not so high. The degree of usual maximum virulence in the ticks of any chosen locality determines the degree of severity of the average local infection in man. The lowest usual level of maximum virulence definitely shown in nature has been in the D. andersoni population on the east side of the Bitterroot valley, where it is seldom that the virus, even though opportunity for "reactivation" has been allowed, produces more than a symptomless, immunizing infection.

There is evidence, as intimated, which suggests to me that tick virus may lose even its power to produce unapparent infection, and that it may still persist in ticks as a specifically unrecognizable microorganism. The evidence to this effect most frequently encountered is in groups of ticks which are all the progeny of one parent female and all of identical history as regards the ingestion of virus and the engorging of subsequent stages. Adults of such groups, tested repeatedly, may fail to show more than a low percentage of demonstrably infected ticks by the most exacting technic, and yet a later test may find 80 to 100 per cent infectious. This phenomenon has not been explained.

It is a fact of considerable interest that the virus of Rocky Mountain spotted fever as carried in nature by the rabbit tick (H. leporispalustris), in contradistinction to that in D. andersoni, *consistently*

produces low grade infections in guinea-pigs (Parker, 1923, 1929). It provokes either unapparent infections, or, if there is a febrile reaction, the fever is commonly low, irregular and of short duration. Therefore, on the west side of the Bitterroot valley, where both ticks are numerous, there is the anomalous situation of two carriers that even meet on the same susceptible host animals, the one with strains of either low or high virulence, the other with those of low virulence. H. leporis-palustris is the only species of tick other than D. andersoni in which virulence has been actually studied.

Demonstration of Rocky Mountain Spotted Fever Virus in Ticks.—When Spencer and Parker began their studies at Hamilton in 1922, the commonly used method of testing ticks for the presence of virus was to feed them on guinea-pigs. If this did not result in infection, it was assumed that the tick was uninfected. It occurred to us that since the virus was present in the infected tick, why should not infection follow if we injected tick tissues into guinea-pigs instead of carrying on the dangerous feeding test? Preliminary experiments with laboratory-infected ticks suggested that the method was feasible. However, when groups of unfed, hibernated adult ticks from nature were thus tested, it was found that even though infected ticks were present, frank infection never resulted. The guinea-pigs into which the ticks had been injected, however, were immune to a subsequent injection of passage virus. On the other hand, when ticks which had been collected from animals were used, that is, ticks which were ingesting fresh blood, typical infection followed. These facts led to the discovery of the phenomenon of "reactivation" (1923), which has been described, and resulted in the adoption of the following method of testing ticks for infection: Ticks to be tested were first fed on a guinea-pig in groups or singly, as conditions demanded, for three days and removed. If the guinea-pig remained afebrile ten days, the recovered ticks were then emulsified in saline solution and injected intraperitoneally into the same guinea-pig. If the latter again remained afebrile for a second ten day period, it was given an injection of passage virus. The following reactions are possible: (1) typical infection following tick feeding; (2) absence of reaction following tick feeding, but typical infection following the injection of tick emulsion; (3) absence of reaction following tick feeding, injection of tick emulsion, and injection of passage virus, indicating an inapparent infection from either the tick feeding or the injection of tick emulsion and (4) absence of reaction following tick indicating an unapparent infection from either the tick feeding or the the injection of the virus. The first three reactions are all diagnostic of Rocky Mountain spotted fever; the last suggests a negative result.

Recently this technic has been modified somewhat for special purposes. We have found, for example, that, when a group of ticks is

allowed to feed on a guinea-pig for three days, infection is transmitted through the host to previously uninfected ticks. This point is possibly of no great significance if tests are being performed merely to determine the presence or the absence of the virus, but if it is desired to secure accurate experimental data concerning individual ticks, the feeding period should be limited so as not to exceed one and one-half days.

Passage of Tick Virus Through the Unabraded Skin.—Spencer and Parker (1930) reported that tick virus causes infection through the mucous membranes and unabraded skin. Blood virus will not. In their experiments, the more concentrated tick virus was diluted until, volume for volume, the tick virus and blood virus contained the same number of infectious doses. When a drop of the tick virus was placed in the conjunctival sac, infection resulted in 50 per cent of their tests; when in the mouth, in 20 per cent; when on the normal skin, in 50 per cent; when on the epilated skin, in 70 per cent, and when on the shaved skin, in 100 per cent. Blood virus similarly applied never resulted in infection. The same concentration of the two types of virus indicated that the difference in infectiousness under the experimental conditions stated was due to some inherent quality of tick virus that is absent in blood virus.

It was felt that this discovery explained the mode of infection of several laboratory-infected persons in whom it had been reasonably certain that tick bite had not occurred. The persons concerned had been engaged in rearing infected ticks for the manufacture of vaccine, and were, therefore, constantly handling engorged larvae and nymphs, which are easily ruptured, with resultant contamination of the hands, either from the ruptured ticks themselves or from contaminated rearing materials.

Difference in Tick Virus and Blood Virus.—One of the important results of our studies of tick virus has been the demonstration of qualitative differences between virus in tick tissues and virus as it occurs in the blood. The more significant differences are:

1. Infectiousness. It has been stated that the infectiousness of tick virus varies markedly. The maximum degree of infectiousness which has been definitely demonstrated indicates that 1 cc. of tick virus may contain 1,500,000 minimum infectious doses for a guinea-pig whereas the same volume of blood virus has never been shown to contain more than 1,000 such doses.

2. Range of virulence. It has been shown that in individual ticks. tick virus may range from a phase of virulence capable of producing only unapparent infections to one that can cause 100 per cent fatality. Strains of blood virus, however, rarely show more than minor variations in virulence even when maintained by animal passage for several years.

3. Infection through the unabraded skin. Tick virus will infect through the unabraded skin, whereas blood virus will not.

4. Tick virus, when killed by certain chemicals, provokes an active immunity, whereas blood virus alone has never been shown to do so, no matter by what method it has been killed or attentuated.

Less work has been done with tissue virus than with either blood virus or tick virus, but the few observations reported here suggest that in some respects at least the properties of tissue virus are intermediate between those of blood and tick virus.

THE VIRUS IN NATURE

Percentage of Ticks That Contain Infectious Virus.—This has been studied mainly in D. andersoni. It varies in different localities and from year to year in the same locality. It may be less than 1 and rarely as high as 5 per cent. In some areas, none can be shown infectious. In tests of several thousand ticks of the species D. variabilis and H. leporispalustris from Minnesota made in 1931 in cooperation with Dr. R. G. Green of the University of Minnesota Medical School, over 1 per cent of the former and 2 per cent of the latter provoked reactions in guinea-pigs which could not be distinguished from those caused by low grade phases of the virus of Rocky Mountain spotted fever.

Virulence of Infectious Virus.—As may be judged from previous sections, infectious virus in nature varies in virulence. Here I am referring to variations in the maximum attainable virulence rather than to variations of virulence in individual ticks. The virus of all infectious ticks of an area may show approximately the same level of virulence (either high or low) or in some it may be low, in others high, and in still others intermediate. Although the maximum level of virulence in any area tends to remain reasonably constant year after year, it is occasionally found to vary within wide limits.

Maintenance and Perpetuation.—Since Rocky Mountain spotted fever is primarily a disease of nature (infection of man being purely accidental), an understanding of the mechanism by which the virus is maintained and perpetuated is of obvious fundamental interest.

So far as western conditions within the range of D. andersoni are concerned, we know that most rodents and certain of the small carnivores are hosts of the larval and nymphal ticks, and that the majority of these small host animals are susceptible to the virus.[1] We also know

1. Although an infected animal has never been demonstrated in nature, we have repeatedly recovered animals the blood of which possessed specific protective properties, and there does not seem to be any reasonable doubt that these susceptible small mammalian hosts become naturally infected. There is no evidence of chronicity however.

that with certain exceptions the adult ticks feed largely, and in some areas almost exclusively, on the larger mammals, both wild and domestic, of which none is susceptible. Also, as previously mentioned, larval, nymphal and adult ticks feed in successive years and infection acquired by larvae or nymphs is passed on to the adult, and that from some females, at least, it is transmitted to their progeny.

On the basis of these points it has been assumed that the virus is perpetuated in somewhat this manner: It survives the winter in infected nymphal or adult ticks. In the spring the infected females engorge (for the most part on nonsusceptible hosts), and from some of them the virus is carried on through the eggs to a part, at least, of the resultant larvae. When one of these recently hatched infected larvae or an infected nymph at the end of winter feeds on a susceptible rodent or small carnivore, the latter becomes infected, and through the medium of this host the virus is acquired by previously uninfected larvae or nymphs. By the next spring the latter have developed to infected nymphs and adults, respectively, which in their turn infect more rodents and again start new lines of tick infection in the same way as before. This is repeated year after year. In this connection, one would imagine that the transmission of the virus from generation to generation through the medium of the eggs of infected females would alone be sufficient to achieve perpetuation, but theoretically, at least, it can be shown that it is unlikely to do so.

I have given here a very sketchy outline of the supposed workings of what is now known to be an extremely complicated process. Indeed, the contributory factors are numerous, and the functional intensity of each one is a variable from focus to focus and even in the same focus within a relatively short period of time and from year to year.

There seems to be no reasonable doubt that the mechanism as described actually operates in nature. However, the basic ideas involved were advanced some years ago when D. andersoni was thought to be the only intermediate host, and when we knew much less than now concerning the bionomics of the virus. Consequently, recent findings relative to the transmission of the virus by other ticks and relative to the range of virulence of tick virus have made necessary a readjustment of the point of view.

The transmission by other ticks does not of itself vitally affect the theory, since, with the necessary modifications for differences in the life cycles and in the host habits of local tick carriers, it can still explain maintenance quite satisfactorily in any area where Rocky Mountain spotted fever occurs. It does appear probable, though, that the mechanism of maintenance can function more smoothly where two or three species of ticks rather than one are involved, particularly since there

are certain hosts on which all three of the proved carriers meet in common. And conversely, the difficulties of control of Rocky Mountain spotted fever by the control of the tick hosts might be correspondingly enhanced. In this connection, however, there is a fundamental question involved; namely, can infection be maintained in any one of these ticks independently of the others or is infection primary in one of the species and secondary in the others? If any one species is a primary host, it would presumably be the rabbit tick, H. leporis-palustris, which is the only one that invariably occurs wherever Rocky Mountain spotted fever is known to be endemic. If this were fact—and it would be possible to present considerable circumstantial evidence to this effect—the control problem would be simplified in some respects. The point is not an easy one to prove, however.

The recent observations relative to the range of virulence of tick virus, however, are of even greater potential fundamental significance in relation to virus maintenance and possible control procedure than the discovery of additional intermediate hosts. The most essential points involved, all of which have previously been mentioned or implied, are: (1) that the demonstrable limits of the virulence of virus in D. andersoni are, on one extreme, low grade, nonsymptom-producing but immunizing infections, and, on the other, typical symptomatic infections that are 100 per cent fatal; (2) that the maximum level of virulence remains essentially constant in any selected local tick population, in some areas approximating the maximum possible virulence, in some that of unapparent infectiousness, while in others it is intermediate; (3) that the virus in any *individual* infected tick of a local tick population can vary in virulence between that of an unapparent infection and the maximum virulence typical of that area; and (4) that there is evidence which suggests that tick virus can lose entirely the quality that enables it to provoke an infection and yet can continue to persist in the ticks as a viable organism capable of regaining its infectiousness under proper stimulus.

It is with the fourth point that I am particularly concerned. It appears certain that the virus of Rocky Mountain spotted fever which has completely lost its infectiousness can temporarily exist as a phase of tick virus in ticks that were originally infected with highly virulent strains. The question of most interest, however, is whether there are strains of the virus that retain this noninfectious characteristic indefinitely, and whether there are areas in which this is the only phase of the virus present, just as there are strains that retain indefinitely the phase of virulence which produces only unapparent infection, and areas in which this is the only phase that can usually be demonstrated. If there are such strains, we are then concerned to know in how high a

proportion of the 95 to 100 per cent (depending on conditions) of any tick population in which infectious virus cannot now be shown they occur. These questions are too involved to discuss further in this paper, but it is desired to point out that if there are such strains of virus, (1) it is quite probable that they are maintained by transfer of the organism from generation to generation through the medium of eggs, and that the previously described mechanism of the maintenance of virus is merely incidental and not essential for the perpetuation of virus, and (2) that if any considerable proportion of ticks contain such strains, this fact would have to be considered in any project or plan that aims to control Rocky Mountain spotted fever through the control of the infection in nature.

The idea that some ticks may contain a noninfectious phase of the virus of Rocky Mountain spotted fever is not entirely new. Ricketts in 1909 advanced a similar hypothesis, which he had reached from an entirely different experimental background.

The extreme view would be that the rickettsia of spotted fever may exist as a "symbiont" in some one or more of the species of tick that transmit it. While there is at this time no justification for taking this possibility too seriously, it may be worth while to mention that there are two rickettsiae, Rickettsia lectularia of the bedbug and Rickettsia melophagi of sheep tick, which are known to occupy this very relationship to their respective hosts.

III. ROCKY MOUNTAIN SPOTTED FEVER IN MAN

GEOGRAPHIC DISTRIBUTION

At the close of the season of 1930, Rocky Mountain spotted fever in man was known to be widespread in Montana, Idaho, Wyoming, eastern and central Oregon, eastern Washington, northeastern California, northern and central Nevada and Utah, and the Rocky Mountain section of Colorado, while a limited number of cases had been reported from southwestern North Dakota, western South Dakota, northwestern Nebraska, northeastern Colorado, northern New Mexico, and a few from southern coast counties of California. In Canada, cases had occurred in south Saskatchewan and possibly in southeastern British Columbia. In 1930, this western region of infection was perhaps three times the size of the known endemic area of twenty-five years before. The extension of its limits had been due, in part, to the addition of sections in which infection has been unquestionably of long standing, but either had not been recognized or had been recognized but not reported, and, in part, to the addition of what had seemed to be new endemic sections.

Early in 1931 Badger, Dyer and Rumreich, of the National Institute of Health, reported cases of the Rocky Mountain spotted fever type as recognized during 1930 in the states of Virginia, Pennsylvania, Delaware, North Carolina and Maryland and in the District of Columbia. Their carefully prepared data are the first conclusive evidence of the occurrence of this disease in the East. There have been rare reports of such occurrence since 1912, but in none, with one exception, was there any confirmatory evidence. The exception was a case reported by Dr. C. R. La Bier of Terre Haute, Ind., in 1925. Serum drawn from his patient six months after recovery was tested at the Hamilton laboratory and found to afford a high degree of protection to guinea-pigs against the highly virulent local type of Rocky Mountain spotted fever. At the time, it did not seem wise to accept the evidence of this test at its face value, but in the light of subsequent developments, there seems no doubt that it should now be considered as confirmatory of the diagnosis, and that Indiana could be added to the list of eastern states in which infection exists.[2]

During 1931 apparently authentic cases were reported from South Carolina, Texas, Louisiana and Tennessee and suspected cases from Arkansas, Missouri, Iowa, Minnesota and Arizona.

Prior to the definite recognition of a type of Rocky Mountain spotted fever in the East, the considerable extension of the known endemic limits in the West had been looked on, although with some degree of reservation, as indicative of a progressive spread of infection in nature. Now, however, the question of whether an actual spread of infection has been involved when cases are reported from an area heretofore supposed to be free from infection is even more obscure. It appears probable that the extent of country involved in the East is indicative of long-established endemicity, and the possibility that infection may have been introduced from the West is one concerning which I am doubtful after sixteen years' study of data relating to supposed spread

2. Such other early reports of suspected cases east of the Rocky Mountain region as are now available were: New York, 1912, Ulster County, 1; 1913, Ulster County, 1, Suffolk County, 3. Minnesota, 1913, Todd County, 1, Becker County, 1. The Minnesota reports and those from Ulster County, New York, were noted by Fricks (Pub. Health. Rep. **29**:449, 1914). No data are at hand concerning the Ulster County cases. With respect to the two Minnesota cases, the reports suggest that one could have been spotted fever, but that the other probably was not. There is available a valuable unpublished account of the Suffolk County, New York, cases, prepared by D. L. Van Dine, at that time with the Federal Bureau of Entomology. So far as this report shows and in view of recent eastern findings, these cases could well have been Rocky Mountain spotted fever. They occurred on Gardner's Island: D. variabilis was abundant, all three of the persons involved had been tick bitten, and the cases all occurred during the season of the year when variabilis transmission is most frequent.

in the Rocky Mountain region. The probable long period during which the disease has gone unrecognized in the East and the isolated possible and probable cases reported from points in the central tier of states during 1931 suggest that discontinuous occurrence across the United States may sooner or later be shown. And in view of these recent new distributional data, it is now my opinion, concerning western conditions, at least, that if a spread of infection has actually taken place, such spread is fully as likely to have been intensive as extensive. In this connection, it is desired to direct attention again to the fact that very low grade virus, incapable of producing recognizable infection in man, can exist for many years in a locality (e. g., the east side of the Bitterroot valley in Montana) without its existence being suspected. If some ecologic factor later results in raising the level of maximum virulence of the local strains of tick virus in such an area, then clinically typical cases may occur and the false impression be given that there has been a spread of infection.

In my opinion, it is entirely probable that the virus of Rocky Mountain spotted fever is widespread in the tick population of this country, and the occurrence of human infection should be considered as a definite possibility wherever any of the ticks occur that have been mentioned as actual or potential carriers to man. This involves a very considerable part of the United States.

INCIDENCE AND PREVALENCE

Most cases of Rocky Mountain spotted fever occur among those groups of the population that secure their livelihood by some outdoor occupation, especially by agriculture. The greatest exposure is probably among sheep-herders and others engaged in handling sheep in the sage-brush areas of the West. However, a considerable proportion of cases occur among those whose exposure is infrequent, such as fishermen, picnickers, tourists, etc. Not infrequently cases occur in city dwellers, owing to the bringing in of infected ticks by some intermediary person or by animals. I have known of cases even in persons who have been bedridden for weeks.

Most infections occur in those of adult age and of the male sex. Both age and sex incidence, however, are largely occupational. In a section such as the Bitterroot valley, where the farm homes are within the actually infected area, the proportion of cases among children is relatively high. In southern Idaho, on the other hand, where the majority of cases are contracted in the sage-brush desert country by persons engaged in the sheep industry, relatively few children become infected. Most cases occur from March through June and the majority during April and May. At higher altitudes (e. g., Wyoming and

Colorado), a higher proportion of cases occur during the latter part of this period. This is the period of activity of the adult D. andersoni. There are occasional cases during the summer and rare ones during the fall and winter months. Although I have no definite data on this point, it appears probable that the proportion of cases occurring during the summer months is likely to be greater in parts of the country in which D. variabilis is the transmitting tick.

Annual incidence depends partly on the abundance of infective ticks, partly on meterologic conditions, and partly on unknown factors. Cold spring seasons or very dry hot ones greatly retard tick activity. Data on western cases accumulated during the past two decades indicate a rather definite cycle of annual prevalence. Peaks have occurred at seven year intervals; namely, in 1915, 1922 and 1929. In each seven year period, between peaks there has been a sharp decrease in cases during the first two years and a slower building up during the last five. The significance of these cycles is not apparent, but they occur both as local and as regional phenomena, although the two may not necessarily coincide. Locally, it is not uncommon for a period of prevalence to be followed by a considerable series of years in which there is a complete absence of human infection.

No marked correlation has been observed between the abundance of ticks and the prevalence of cases. It is probable that prevalence of infection, other factors being equal, is more closely related to the percentage of ticks containing symptom-provoking virus than to tick abundance.

The actual number of cases that occur annually is problematic. The average number in the West has frequently been estimated at 750. Certainly this number is not on record, but on the one hand it is known that many cases are not reported, and, on the other, it is equally certain that some typical cases are incorrectly diagnosed and that many mild ones are not recognized. There have unquestionably been more cases in Idaho than in any other state. Formerly, there were frequently 300 to 400 each year, but this number has dropped materially during the last decade. It is likely conservative to estimate that 10,000 cases have occurred in this state. In the East, Rumreich, Dyer and Badger record 93 cases in 1930. In 1931 there were 40 cases in the State of Maryland and 11 in the District of Columbia.

It is probable that infection seldom dies out of a locality unless agriculture becomes so highly intensified that the wild mammal hosts necessary to maintain a tick population are essentially exterminated. As agriculture develops in the West, there is likely to be a drop in prevalence in some areas and an increase in others, depending on such factors as the type of agriculture and the characteristics of the natural

environment. Certain it is that the prevalence of infection in some sections is directly traceable to the activities of man attendant on development of the county.

MECHANISM OF HUMAN INFECTION

So far as known there is no evidence that infection in man is ever acquired from nature except through the medium of ticks. The usual mode of transmission is certainly by tick bite. However, the evidence of Spencer and Parker (1930) that tick virus will infect through the unabraded skin and the conjunctival sac of guinea-pigs suggests that the infection of man in this way is a possibility, and it doubtless occasionally occurs. The opportunity for infection in this manner could result from the common practice of picking ticks by hand from dogs and other domestic animals with the attendant danger of rupturing the tick and contaminating the fingers with tick virus. Such virus could then be rubbed on the skin of some unprotected portion of the body or into the eye.

I have demonstrated that tick excrement is occasionally infectious, but experimental studies to determine whether or not the virus as it occurs in tick excrement will infect through the unabraded skin have proved negative. It appears improbable that infection occurs in this manner.

RELATION OF THE PHENOMENON OF REACTIVATION TO INFECTION IN MAN

In the discussion of tick virus, mention was made of the fact that the virus of Rocky Mountain spotted fever in ticks at the end of winter is present as a nonsymptom-producing and frequently immunizing virus, and that it does not produce symptomatically recognizable infections until its level of virulence is raised, either by heat or by the ingestion of blood. This point has an important bearing on infection in man, for the reason that it is a matter of some hours and not infrequently of a day or more after tick attachment before reactivation occurs. The shortest recorded interval is one and three quarter hours (Ricketts), and I have known instances in which the host was not infected after three days' feeding, although the same ticks were later proved to contain highly virulent virus by injection into guinea-pigs. It is obvious, therefore, that if a tick which has become attached is removed within a few hours, the danger of infection is materially minimized.

I believe that this phenomenon of reactivation also has a bearing on an epidemiologic condition that has been observed repeatedly in the Bitterroot valley; namely, that it is seldom that cases of Rocky Mountain spotted fever are reported until several weeks or even a month

or more after the ticks first appear. It is true that in some localities there is less exposure in the early spring, but there are others in which this is not so. This point was puzzling for a number of years, but it now seems likely that in the early spring when the virus in the recently emerged ticks is at its lowest ebb of infectiousness, and while the days and the nights are still cool, it takes so long for the virus to become reactivated after a tick has become attached that it is usually detected and removed before the virus has become virulent. Later in the season, however, the accumulated temperature has apparently resulted in a partial reactivation of the virus, and a tick once attached can presumably infect more quickly, with a resultant increase in the number of instances in which infection is accomplished before removal of the tick.

VIRULENCE

As mentioned, the severity of infection in man varies in different localities, but is usually reasonably constant in any selected section for prolonged periods. In western Montana, about 90 per cent of cases in persons of adult age are fatal, and approximately 50 per cent of those in children, the inclusive rate being close to 75 per cent. In the Bitterroot valley there have probably been over 400 deaths from Rocky Mountain spotted fever. Formerly, this was supposed to be the only area of excessively high death rate, but we now know that there are sections with death rates equally high in parts of Idaho and Wyoming, and possibly Oregon. The percentage of fatality in cases of this disease in some of the western states over a series of years has been as follows (Parker, 1929): Montana, 26.91; Wyoming, 21.44; Colorado, 20; Oregon, 18.94; Nevada, 16.42; Washington, 11.90; California, 11.59; Utah, 6.89, and Idaho, 4.16.

Rumreich, Dyer and Badger reported a fatality of 22.6 per cent among the 93 cases reported in the eastern states in 1930. In some foci no deaths have ever been reported.

In southern Idaho and eastern Oregon, ambulatory cases are occasionally reported. In these the typical eruption is present, but it is not abundant and may even be localized. Some physicians claim, and it is probably true, that there are still milder cases without eruption. The diagnosis of such cases, however, is largely presumptive.

Physicians who have lived in infected areas for many years, and who have treated considerable numbers of patients, sometimes several hundred, have inclined to the opinion that there are certain years during which virulence is increased above the usual level for the particular locality concerned. Others, and they are rather numerous, believe that there has been a gradual increase in virulence up to the present time. These points are difficult to decide on the basis of available data.

DURATION OF ACTIVE IMMUNITY AND SECOND INFECTIONS

It has been assumed generally that a permanent immunity results after recovery from Rocky Mountain spotted fever, however mild. This assumption has led to the discounting of reports of second infections, especially since no instance has ever been encountered in which the patient was treated by the same physician during both illnesses. Furthermore, it is known that in former years, before the two diseases were differentiated, tick-caused tularemia was occasionally reported as spotted fever. In fact, I have talked with persons that claimed to have had "both types of spotted fever, the eruptive and the glandular." Such confusion was not surprising prior to the discovery of tularemia as a specific disease. Recently, however, a few instances of seemingly unquestionable second infections have come to my attention. There is even an instance of a reputed third infection. In view of these reports and of the results of laboratory tests which suggest that in guinea-pigs, at least, there is a correlation between the severity of infection and the degree and duration of the resultant immunity, it now seems advisable to recognize the possibility of reinfection.

Most instances of reputed second infections have been from those parts of the West in which a high percentage of cases occur among men who handle sheep on the range. Certain it is that the opportunity for second infections among such persons is greatly exaggerated because of the fact that during the tick season they live on the open range and are exposed both night and day, not for a portion of the day only, as in most occupations.

LABORATORY AIDS TO DIAGNOSIS

One of the lines of work being carried on at Hamilton concerns the place of laboratory tests in the diagnosis of Rocky Mountain spotted fever. There are several reasons why this study is desirable, even though Rocky Mountain spotted fever has been considered as a distinctive and easily recognized disease: 1. There are frequent cases in which the diagnosis is in doubt because of atypical findings. 2. An increasing variety of typhus-like diseases are being recognized in various parts of the world, suggesting the possibility that forms other than Rocky Mountain spotted fever occur in part, at least, of the Rocky Mountain region. 3. Laboratory confirmation of diagnosis is of distinct value to physicians in areas in which cases are infrequent.

The three tests being used in identification at Hamilton at present are the following:

1. An infection test in which guinea-pigs, which are very susceptible to Rocky Mountain spotted fever, are given injections of blood of a

patient acutely ill; they commonly show a diagnostic reaction to the virus of Rocky Mountain spotted fever.

2. A test for agglutination of Bacillus proteus X organisms by Rocky Mountain spotted fever serum.

3. A protection test made by injecting mixtures of convalescent serum and virus into guinea-pigs.

Infection Test.—It is usually possible to reproduce typical Rocky Mountain spotted fever by injecting 1 cc. of a patient's blood intraperitoneally into a male guinea-pig. Males are used because of the characteristic scrotal reaction, which is more consistently produced if the injection is made into the posterior portion of the abdomen.

This is the preferred test if the case concerned is of *at least moderate severity,* if the sample is taken before lysis begins, and if the blood can be injected within a few hours. It is less valuable in relatively mild cases (see "Protection Test") or for testing blood which has been two or more days in the mail.

The inoculated guinea-pig may show both fever and typical scrotal lesions or fever without lesions, or it may remain afebrile. In any event, surviving guinea-pigs should later be given an injection of potent virus. If an infection following the original injection of blood is typical of Rocky Mountain spotted fever, and the guinea-pig recovers, the subsequent immunity test serves as a desirable check on specificity. If, as sometimes happens, there is fever only, then the later injection of virus is an essential part of the diagnostic procedure. Finally, if the guinea-pig remains afebrile, the immunity test is still necessary, since the original injection of blood sometimes produces an unapparent infection.

A negative test is suggested if the guinea-pig remains afebrile following the injection of blood and typical Rocky Mountain spotted fever follows the immunity test. Even this result must be accepted with reservations so far as its being a basis for a definite negative diagnosis is concerned.

Anomalous reactions are certain to occur in any considerable series of tests, and such results can be safely interpreted only in the light of wide experience. Reactions of uncertain interpretation are most likely to occur when testing blood from patients with relatively mild cases.

If the case concerned is in a section of the country where there is danger of confusion with endemic typhus, multiple guinea-pigs should be used if possible, and both the virus of Rocky Mountain spotted fever and that of endemic typhus used for immunity tests of possible survivors. It may even be necessary to make brain sections for histologic examination.

Agglutination Test.—Many Rocky Mountain spotted fever serums taken late in the course of the disease or during early convalescence agglutinate proteus X 2 or one or more strains of proteus X 19, or both.

As thus far studied, the following conditions tend to discount somewhat the usefulness of this test:

1. The affinities of the agglutinins of Rocky Mountain spotted fever serums for proteus X organisms are broader than those of the agglutinins of typhus serums. Besides X 2, it has thus far proved necessary to use several strains of X 19, and it is not feasible as yet to designate any one strain or any particular group of strains as the most advantageous for routine tests. Negative agglutination of a few strains does not mean that a positive result would not have been secured had additional strains been used.

2. A considerable proportion of Rocky Mountain spotted fever serums, even when taken at the most favorable period, do not cause agglutination in sufficiently high titer to be significant.

3. Occasionally, supposed normal serums (so far as Rocky Mountain spotted fever is concerned) cause agglutination in as high titer as occurs in many definite cases.

In spite of these faults, which will perhaps be obviated in part, at least, by further research, it is felt that this test is of considerable value.

To be most instructive, a series of three blood samples should be tested in each case. The first should be taken as soon as the nature of the infection is suspected or when the rash first appears, the second between the tenth and fifteenth days, preferably about the twelfth, and the third during early convalescence. In such a series, a positive test is indicated by an increasing titer of agglutinins. This is sometimes accompanied by an increased affinity for proteus X strains.

Protection Test.—Tests of early convalescent serum to determine its protective value against the virus of Rocky Mountain spotted fever obtained by passage through guinea-pigs are usually of diagnostic value, if the case is of ordinary severity. Duplicate mixtures are prepared containing 0.5 cc. of convalescent serum and 0.1, 0.25 and 0.50 cc. of serum virus, respectively. After standing half an hour at room temperature, these mixtures are injected into guinea-pigs intraperitoneally. Control animals receive corresponding amounts of virus.

It is hoped that this test will prove of value in the diagnosis of relatively mild cases for which the other two tests are often inconclusive, but it has not yet been sufficiently used for this purpose to warrant a definite statement.

In general, it is inadvisable to use whole blood virus for this test if highly fatal strains of passage virus such as are maintained at Hamil-

ton are employed. The whole blood virus of these highly virulent strains is frequently so potent that the definite protective properties of the convalescent serum may be overwhelmed and an apparent negative result secured. The less potent serum virus is therefore used. It is also important not to use excessive amounts of virus.

The protection test is also of value in differentiating between Rocky Mountain spotted fever and other typhus-like infections.

IV. CONTROL AND PREVENTION

The control of Rocky Mountain spotted fever by the control of the transmitting agent has been attempted only in Bitterroot valley in western Montana. The main measures employed have been dipping, grazing control, and the control of rodents. This work was begun in 1911, and from a small beginning it has gradually extended until it now covers most of the west side of the valley. Although definite local good has been accomplished, the results during the past twenty-one years have been discouraging as far as the feasibility of the measures of tick control for use over any extended era of the country is concerned. This has been due in part to natural obstacles difficult to overcome, in part to lack of permanence of results, and in part to the fact that control procedure has been based on a too superficial knowledge of the relative importance of the various factors of the local complex that controls maintenance.

A few years ago the Montana State Board of Entomology took up the study of the parasites of ticks in the hope that the parasites might prove to be a means of tick control that could be used over wide areas in any section of the United States. These studies have been taken over temporarily by the Public Health Service. While the resulting data have thus far been none too encouraging, it is very desirable that experimental studies be carried to such a point that it can be learned definitely whether parasites will or will not be useful as an agency of tick control.

Because there is no practical procedure in tick control, prevention of Rocky Mountain spotted fever must depend primarily on personal prophylaxis and vaccination.

The two most essential requisites of personal prophylaxis are (1) the avoidance of tick bites, and (2) the early removal of any ticks that may escape attention and become attached. The discussion of these points which follows applies particularly to western conditions and the habits of the Rocky Mountain wood tick, D. andersoni.

The first consideration in the avoidance of tick bite is to keep out of known tick-infested areas during the spring and early summer. When this is not practical, the next best procedure is the wearing of suit-

able clothing. Ticks ordinarily are found on grass and low vegetation and are only occasionally more than 18 inches (46 cm.) from the ground. It is, therefore, important that the type of clothing should be such that ticks will be prevented from crawling inside the trousers from the bottom. This may be accomplished by wearing high boots, leggings, puttees or socks outside the trousers legs. Under these conditions, most ticks will crawl up the outside surface of the clothing, and if not discovered before, will often make their presence known when they come in contact with the short hairs on the neck. When in dangerous country, the habit of passing the hand over the neck occasionally to feel for ticks is a good one to acquire. The texture of the clothing is also a matter of importance, since ticks are more likely to secure a hold on rough clothing than on that of smoother finish. There are advantages in both types, however. Clothing with a heavy nap, although more likely to pick up ticks, greatly slows down their movements, and this factor is particularly advantageous when socks are worn outside the trousers legs. If socks are white, the ticks are easily seen and may be removed before they crawl to the clothing above. For other outside apparel a smooth finish is perhaps preferable, since fewer ticks will secure a hold thereon, and those that do are more easily brushed off. On the other hand, they can crawl up more rapidly.

If exposure is marked or continuous, a certain number of ticks will reach the body of the average person in spite of all precautions. It is therefore essential that the aforementioned measures should be supplemented by the examination of the inside of the clothing and the body. Since ticks seldom attach themselves immediately, unless late in the season, and are seldom infectious until after attached several hours, examination made twice each day will ordinarily be sufficient. In areas known to be heavily tick-infested or particularly dangerous, however, it should be more frequent. The time of day of such examination will depend, to a considerable degree, on occupation and individual habit as regards the changing of clothing. One examination, however, should always be made on retiring, and the complete removal of clothing is most desirable. Parts of the body which cannot be seen should be thoroughly explored with the hands, paying particular attention to the hairy portions. Removed clothing should not be placed on the bedding, since any ticks which have escaped inspection are likely to crawl to the sleeping person. If two persons are occupying the same bed, particular precautions should be taken, since a considerable number of instances are on record of two persons being infected by the same tick under these conditions. An enhanced danger to the second person arises from the fact that if the tick concerned becomes dislodged from the first and attaches itself to the second, the virus having been "reactivated,"

transmission of infection to the latter can take place in a very short time. One instance is known of the same tick infecting three persons under these conditions.

When it is necessary to sleep in the open, an additional precaution must be taken with respect to the placing of the tent or bedding, as the case may be. Since ticks are usually most numerous where small animal hosts are most prevalent, areas well populated with rodents should be avoided. Standing timber is probably the safest camping ground, especially where low vegetation is scanty. In the mountainous areas, at least, ticks tend to concentrate, sometimes in immense numbers, along suitably located trails and roads, especially old wagon roads with low brush at the sides, or strips of grass or weeds in the middle. Such locations are especially to be avoided. In sage-brush sections, avoid sage-brush.

Because of the mentioned habit of the adults of D. andersoni of concentrating along trails and roads, persons walking along these should be particularly watchful. In the mountainous areas this is especially true on trails that cross slopes or follow along the foot of slopes.

One encounters many residents and physicians of tick-infested areas who offer various methods of procedure for the removal of attached ticks. The simplest procedure for the average person outdoors to follow is to grasp the tick lightly between the thumb and forefinger and pull it loose. The idea that one should wait until the tick can be removed by a physician is a poor one. In the first place, the quickest possible detachment of the tick is far better insurance against infection than any delayed surgical removal can possibly be, and, in the second, the idea that there is danger of leaving the mouth parts in the skin is largely erroneous. The practice of applying a sterilizing or cauterizing agent at the site of the tick bite is perhaps better founded, although how much actual good is accomplished thereby is problematic. Probably the value of such applications lies in the possible prevention of secondary infection rather than in the prevention of the transmission of a tick-borne disease. In our experience, the most satisfactory agent of this kind for outdoor use is silver nitrate in the form of a caustic pencil.

No satisfactory substance is known which can be placed on the clothing or body to repel ticks. Certain oils are effective, but are not practical.

The means of prevention thus far discussed are unfortunately not 100 per cent effective, and persons subjected to any considerable degree of exposure should be advised to take the vaccine which is prepared by the Public Health Service. Seven years' use indicates that this vaccine affords complete protection in the average person against the milder

strains of Rocky Mountain spotted fever, and against the highly fatal strains, a sufficient measure of protection to ameliorate greatly the usual very severe course of infection and to insure recovery. This vaccine is prepared from infected ticks and is difficult and expensive to produce. It is manufactured only at the United States Public Health Service Laboratory at Hamilton, and is dispensed to physicians without charge. The average person is protected for only one tick season and revaccination each year is necessary.

Notes and News

University News, Promotions, Resignations, Appointments, etc.—Charles Weiss, formerly associate professor of applied bacteriology and immunology at Washington University School of Medicine, has been appointed director of the Clinical and Research Laboratories of the Mount Zion Hospital, San Francisco.

The gold Paul Ehrlich Medal has been awarded to Paul Uhlenhuth, professor of hygiene and bacteriology at the University of Freiburg, Baden.

The Bernhard Nocht Medal has been awarded to Hans Ziemann, professor of parasitology at the University of Berlin.

The Cameron Prize of the University of Edinburgh has been awarded to Dr. George F. Dick and Dr. Gladys H. Dick, Chicago, in recognition of their work on the etiology and treatment of scarlet fever. The award is made annually "to a person who, in the course of the five years immediately preceding, has made any highly important and valuable addition to practical therapeutics."

Having reached the age limit, Frank B. Mallory has retired as pathologist to the Boston City Hospital. His successor is Frederic Parker, Jr. The new pathologic laboratory of the hospital will be known as the Frank B. Mallory Pathological Institute.

Lewis R. Hill has been appointed professor of bacteriology in the school of medicine of Loyola University, Chicago.

Frank C. Mann, Mayo Foundation, Rochester, Minn., has been awarded the 1932 Gerhard gold medal of the Pathological Society of Philadelphia.

Society News.—The annual meeting of the American Association of Immunologists will be held in Washington, D. C., on May 9 and 10, 1933. The usual session with the American Association of Pathologists and Bacteriologists, which meets at the same time and place, will not be held this year.

The officers of the Pathological Society of Philadelphia for 1933 are: V. H. Moon, president; Morton McCutcheon, vice president, and H. L. Ratcliffe, secretary-treasurer.

The Federation of American Societies for Experimental Biology will meet in Cincinnati, Ohio, on April 10, 11 and 12, 1933.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

THE CHANGES PRODUCED IN THE BLOOD PICTURE BY REMOVAL OF THE NORMAL MAMMALIAN SPLEEN. E. B. KRUMBHAAR, Am. J. M. Sc. **184**:215, 1932.

In the normal mammal, splenectomy causes a true, mild temporary anemia that varies both in individuals and in species and in time of appearance, degree and duration. This is accompanied by an increase in the reticulocyte count and an increase in the resistance of the erythrocytes, both of which are apparently responses to the anemia. This anemia is due to a loss with the spleen of a property which aids the formation of erythrocytes, such as the conservation of the iron of broken-down erythrocytes. This function is eventually taken over, at least in large part, by other members of the reticulo-endothelial system. The normal spleen does not have an inhibitory action on erythropoiesis in the bone marrow. The reason for the appearance of Jolly bodies and nucleated forms, which has been reported by the majority of investigators, has not been explained. It is possible that they represent a loss with the spleen of a property of maturing erythrocytes, rather than the loss of a brake on erythrocytopoiesis. The cellular hyperplasia in the bone marrow observed after splenectomy represents not only the compensatory response to the anemia, but the loss of an important organ concerned with hemolysis; that is, many of these hyperplastic cells are functioning on the hemolytic side of the hemolytopoietic system. Splenectomy both in normal animals and in cases of thrombopenic purpura causes a marked rise in the platelet count, which is more persistent than other postoperative thrombocytoses. It has not yet been settled whether this is due to the removal of a platelet death-house or of an organ that tends to inhibit platelet formation or to both.

AUTHOR'S SUMMARY.

THE ABSENCE OF OSTEOPOROSIS DEMONSTRATED CHEMICALLY IN CLINICAL HYPERTHYROIDISM. ARNOLD E. OSTERBERG and RALPH G. MILLS, Am. J. M. Sc. **184**:399, 1932.

It has been shown previously that hyperthyroidism may produce the excretion of endogenous calcium, which may result in osteoporosis demonstrable by roentgenogram. In this study, chemical and roentgenographic study of bone, removed post mortem from twenty-three patients who had had histories of hyperthyroidism, and from seventy-eight control subjects, failed to demonstrate a sufficiently constant difference in the percentage of ash, percentage of calcium, calcium-phosphorus ratio or roentgenographic opacity to warrant a conclusion that hyperthyroidism is always accompanied by some degree of osteoporosis. Failure to demonstrate a difference may be explained by assuming that there was compensatory ingestion of calcium or other variable factors that may occur in clinical hyperthyroidism. Obviously, ingestion of calcium is not controlled in clinical hyperthyroidism as it may be controlled in experimental hyperthyroidism. Further work of this nature in clinical hyperthyroidism seems unnecessary, since the results apparently can be only inconclusive.

AUTHORS' SUMMARY.

VARIATIONS IN THE TOTAL BLOOD LIPID IN ALIMENTARY LIPEMIA. H. F. WECHSLER, Arch. Int. Med. **50**:37, 1932.

The total blood lipid curves after the ingestion of 100 cc. of olive oil in sixty-seven subjects who were apparently free from pancreatic or hepatic disease are presented. The curves could be subdivided into three categories: ascending, 63.2 per cent; flat, 17.5 per cent, and descending, 19.3 per cent. The age of the subject

and the presence of arteriosclerosis markedly influenced the total blood lipid. Persons in the second and third decades presented a flat curve; those in the fourth, fifth and sixth decades an ascending curve, and those showing evidence of arteriosclerosis a flat or descending curve. Starvation produced a moderate progressive rise in the total blood lipid. Dextrose eliminated the starvation effect.

AUTHOR'S SUMMARY.

LYMPH PRESSURES IN STERILE INFLAMMATION. M. E. FIELD, C. K. DRINKER and J. C. WHITE, J. Exper. Med. **56**:363, 1932.

The normal lymph pressure in the legs of anesthetized dogs is not measurable. The maximum pressure in the quiescent leg under conditions of sterile inflammation is about 120 cm. of lymph. Venous pressure rises immediately in a region subjected to sterile inflammation and then slowly returns to normal. The rise in lymph pressure follows the rise in venous pressure. Changes in lymph flow, lymph pressure and protein concentration of the lymph occur when the part producing lymph is subjected to external temperatures between 50 and 60 C.

AUTHORS' SUMMARY.

GASTRIC ULCER IN ALBINO RATS DEPRIVED OF VITAMIN B (B_1). G. DALLDORF and M. KELLOGG, J. Exper. Med. **56**:391, 1932.

In albino rats deprived of vitamin B ulcers of the gastric mucosa commonly develop.

AUTHORS' SUMMARY.

MARROW HYPERPLASIA AND HEMOGLOBIN RESERVE IN ANEMIA DUE TO BLEEDING. L. W. F. OEHLBECK, F. S. ROBSCHEIT-ROBBINS and G. H. WHIPPLE, J. Exper. Med. **56**:425, 1932.

In long continued, severe anemia due to bleeding in dogs one may observe all degrees of red marrow spread. The maximal red marrow spread takes in the total marrow area in the ribs, vertebrae and long bones. The minimal red marrow spread may involve only from 10 to 20 per cent of this maximal area. All gradations between these extremes are observed in this series. The extent of the red marrow spread is not dependent on the length of the period of anemia, nor is it related to the capacity of the dog to produce new hemoglobin and red cells on standard diets. Evidence points to the liver as being concerned with this production of hemoglobin, and liver function may set the limits for the production of hemoglobin on these standard diets. This, in turn may determine the needful red marrow spread. During favorable diet periods there is a storage of hemoglobin or hemoglobin precursors which emerge later in the control periods as finished red cells. This reserve of hemoglobin-producing material is not stored as mature red cells in the marrow or elsewhere but as intermediates stored probably in the liver and red marrow but also perhaps in the kidney and spleen. Red marrow rarely gives evidence of exhaustion even after many years of continuous severe anemia. This would seem to consist of a shrinkage of the red marrow area rather than a degenerative change of the red marrow cells. The spleen shows some evidence of erythrogenesis in these dogs. Megakaryocytes in some instances are conspicuous, and nests of nucleated red cells are found in the spleen pulp, but it is unlikely that the spleen contributes a large amount of red cells to the anemic circulation in the experiments. There is no evidence that erythrogenesis ocurs in the liver or lymphatic tissue in these dogs.

AUTHORS' SUMMARY.

THE INFLUENCE OF PLASMA PROTEIN ON THE CHLORIDE CONTENT OF THE CEREBROSPINAL FLUID. H. I. COOMBS and K. W. THOMPSON, J. Exper. Med. **56**:449, 1932.

When the plasma protein of dogs is lowered by plasmapheresis, the concentration of chloride and sodium in the plasma and that in the cerebrospinal fluid tend

to become the same, a diminishing of the usual disparity which exists in the presence of a normal plasma protein. This is in accord with the theory that the cerebrospinal fluid is a dialysate, the choroid plexus acting as a simple dialyzing membrane.

AUTHORS' SUMMARY.

PEPTIC ULCERS AND THE INTERBRAIN. H. CUSHING, Surg., Gynec. & Obst. **55**:1, 1932.

This article deals extensively with perforated and other lesions in the esophagus, stomach and duodenum connected with injury and disease of the basal regions of the brain. It reviews critically the literature on the neurogenic origin of peptic ulcer, and reports three fatal instances of acute perforated lesions after operations for cerebellar tumor.

FROM THE AUTHOR'S SUMMARY.

EXPERIMENTAL INFLAMMATION OF THE COLON: (A) RELATIONSHIP OF MUCUS PRODUCTION IN GOBLET-CELLS TO THE GOLGI APPARATUS; (B) MITOCHONDRAL CHANGES. HOWARD FLOREY, Brit. J. Exper. Path. **13**:349, 1932.

Some light on the question as to whether ordinary epithelial cells can become goblets is given by these observations. The following interpretation of the observations is given: Toward the bases of the crypts an indifferent type of cell exists; some of these cells start to elaborate mucus in the region of the Golgi body. These mucus cells are indistinguishable histologically from the epithelial cells, except by their mucus, as is clearly seen in both the rat and the cat. During their maturation, these cells pass toward the lumen of the intestine (Bizzozero's therapy), and it is then that the protoplasm and nuclear differences here described appear. These differences, once acquired, persist, as is seen in the surface epithelium of the rat's colon and the artificially exhausted goblet cells of the cat. On the evidence gathered from these preparations, it is not considered probable that the goblet cells revert to cells completely indistinguishable from the epithelial cells, though they may acquire a striated border. In other words, the goblet cell has become a distinct entity, although starting from an indifferent cell. The mitochondrial differences between the goblet cells in the exhausted cat colon and the epithelial cells are marked, but this is not perhaps a permanently distinctive feature, because the massive mitochondria apparently reform into filaments. In the rat no difference was seen in the mitochondrial content of the two types of young cells. With regard to another disputed point, evidence has been obtained. The question has been long debated whether a goblet cell, once having been evacuated, can elaborate a further amount of mucus. In a freshly stimulated colon, goblet cells can be found which are clearly almost completely exhausted of their previous content, but in which granules are present just above the nucleus. This same division into a zone of granules just above the nucleus and a discharging tip of the cell is well seen in the normal rat colon and rabbit colon. A reasonable interpretation in these cases is that the mucus cell is elaborating a further supply of mucus during discharge. This view is strongly reenforced by experiments in which the animal was allowed to recover for twenty-four hours after exhaustion produced by the administration of mustard oil. The conclusion is reached that a goblet cell may be manufacturing mucus in the Golgi area at the same time that it is being discharged at its apical border. From the mitochondrial preparations no support has been obtained for the view that the mitochondria participate in elaboration of the mucus. From the fact that in the rapidly exhausted goblet cell mitochondrial substance reappears in large masses, it would seem probable that during the filling of the cell with mucus the chondriome is compressed together so that the mitochondria coalesce. With the relief of pressure these masses are capable of reassuming filamentous form in which transition stages can be seen. The interpretation of the other mitochondrial changes is more difficult. Perhaps they represent an increased production and altered orientation under the inflammatory stimulus.

FROM THE AUTHOR'S SUMMARY.

LIGATION OF THE COMMON BILE DUCT. G. R. CAMERON and C. L. OAKLEY, J. Path. & Bact. **35**:769, 1932.

Hyperplasia of the bile ducts with biliary stasis and dilatation of the bile passages follows on sudden occlusion of the common bile duct. New bile ducts bud off from the interlobular ducts and grow around and between the hepatic lobules, causing atrophy, with consequent hyperplasia of the liver cells. In the rat, by the third week there is considerable disorganization of the liver, with islands of regenerating and atrophying cells surrounded by broad bands of newly formed bile ducts and a small amount of supporting fibrous tissue. The common bile duct dilates to form a large sac containing bile under considerable tension, displacing and compressing adjacent structures. In the rat, guinea-pig and rabbit, focal necroses in close association with the portal canals are seen throughout the period of survival. They are preceded by congestion of the sinusoids of the affected areas, with "hyaline" degeneration (*dégénération vitreuse* of Charcot and Gombault) of liver cell columns. Healing occurs by resorption and regeneration of liver cells, generally without the formation of scar tissue. In the absence of infection, fibrosis does not occur, the amount of fibrous tissue developing in the portal canals not exceeding that necessary to support the new bile ducts, as judged from the quantity normally present in Glisson's capsule. A completely divided common bile duct may undergo reconstruction, so that there is reestablishment of the biliary flow. The liver then returns to its normal condition. Two accidents are not uncommon in the rat after ligation of the common bile duct: (1) perforation of the dilated common bile duct, with or without necrosis of the abdominal fat which generally occurs during the first fortnight, and (2) venous thrombosis with infarction of part of the liver, which occurs during the second and third weeks.

AUTHORS' SUMMARY.

THE INFLUENCE OF THE VESTIBULAR NERVES AND IN PARTICULAR THE NERVES OF DEITERS ON THE TENDON REFLEXES. PAUL MARTIN, Arch. internat. de méd. expér. **7**:191, 1932.

The destruction of the nerves of Deiters or the severing of the deiterospinal bundle gives the appearance in a decerebrated cat, of hypotonia and a change of the tendon reflexes which simulate the reflexes of an animal in which the dorsal medulla has been severed. Only the lesions of Deiters' nerves and of its efferent fibers, to the exclusion of other bulbar complexes, determine this change of these reflexes. The elongation of the myograms of patellar reflexes which determine the spinalization or the destruction of Deiters' nerves or of its motor fibers is the result of the abolishment of tone and of the modification which results from the initial length of the muscle fibers participating in the tendon reflexes. The length of the isometric myogram of a tendon reflex appears to constitute, all other conditions being equal, an indirect measure of the degree of muscle tone elicited. The abolishment of tendon reflexes, in man, can result from a lesion or from a functional alteration of Deiters' nerves. In a patient with a tumor of the posteriocerebral fossa, it should be considered as a sign which is the result of bulbar involvement and consequently as an alarming symptom.

AUTHOR'S SUMMARY.

THE CONTRACTILITY OF BLOOD CAPILLARIES (ANATOMIC RESEARCHES). LEON STIENON, Arch. internat. de méd. expér. **7**:231, 1932.

The cells of Rouget, such as the pericytes, and adventitial cells, are not muscle cells but indifferent elements of mesenchymal origin (Maximow). The pericytes, clinging to the walls of the capillaries, interlacing with their prolongations, can by their ameboid movement narrow the caliber and even completely close the vessel. The pericytes, endowed with only an inferior contractility, can from a functional point of view be compared with the muscular fiber cells of arteries and veins. No observations actually demonstrate the connection of the pericytes with the nervous system.

AUTHOR'S SUMMARY.

THE PATHOLOGY OF PULMONARY INSUFFICIENCY. H. VELLGUTH, Beitr. z. path. Anat. u. z. allg. Path. **80**:517, 1931.

Pulmonary insufficiency is the rarest of all valvular diseases, and is almost always acquired. The location of an inflammation on the pulmonary valve is aided by an increase in right ventricular pressure, as in interventricular septum defect, increased peripheral resistance in the pulmonary circuit, chronic pulmonary tuberculosis and mitral stenosis.

Pulmonary insufficiency is compensated for with difficulty, and death occurs early if functional tricuspid insufficiency is added thereto. In the more chronic cases the hypertrophy of the right side of the heart leads to the rotation of the heart from right to left, so that the right ventricle forms the anterior surface and the left border of the heart.

W. S. BOIKAN.

EXPERIMENTAL SCLEROSIS OF THE PORTAL VEIN. A. SEMETZ and W. MICHELEWA, Frankfurt. Ztschr. f. Path. **43**:167, 1932.

Rabbits were fed with various amounts of cholesterol from one to two and one-half months. In several instances, a thickening of the intima of the portal vein was found grossly. Histologically, the intima revealed swollen endothelial cells containing globules of fat, some of which were doubly refractile lipoids. The intima was thickened and fibrosed in portions. The media consisted of thickened elastic lamellae. The authors believe that the changes in the portal vein are similar to those described in the large arteries by Anitschkow and others who fed animals with cholesterol.

O. SAPHIR.

EFFECT OF VITAMIN D ON BONE. M. SCHMIDTMANN, Virchows Arch. f. path. Anat. **280**:1, 1931.

The author propounds two problems for solution: 1. Is the healing of lesions of the bones in experimental rickets brought about by the administration of vitamin D identical with that described by Schmorl in the spontaneous healing of rickets in human beings? 2. Has vitamin D in the form of viosterol (vigantol) any effect on the normal bone of experimental animals? The effects of the oil on normal bone were studied in young growing rats and rabbits and in adult rats, rabbits and cats. Young rats were used for the study of the healing process of experimental rickets under the influence of vitamin D. The effects of the vitamin on normal bone differ in the young and in the adult animal. In the young, the marrow is hyperemic; newly formed capillaries grow from the marrow into the epiphyseal cartilage; the zone of proliferating cartilage is decreased in width, and the matrix of the cartilage becomes calcified. In the young animal with rickets, the process is identical with that which occurs in the normal bone of young animals, but is more marked. This process is not identical with that of the spontaneous healing of rickets in human beings. Although the bone may appear normal roentgenologically, histologically normal bone is not formed until a considerable time after the administration of vitamin D has ceased. In the normal bone of adult animals, histologic changes were not uniformly produced by the administration of viosterol. Those that did occur were of two kinds. After a short period of administration the calcium content of the bone may be increased. The trabeculae of the spongiosa are broader than normal, and the cortex is increased in thickness. After prolonged administration, the calcium content of the bone is decreased; the bone becomes thinner and softer; the marrow becomes fibrous; the bone is decreased in amount in proportion to the altered marrow, and spontaneous fractures may occur.

O. T. SCHULTZ.

THE EFFECT OF PITUITARY ANTERIOR LOBE HORMONE ON THE TESTIS. H. BOETERS, Virchows Arch. f. path. Anat. **280**:215, 1931.

Boeters' experiments were undertaken for the purpose of determining whether the hormone of the pituitary anterior lobe causes changes in the male germ cells

that might form the basis for studying the effects of such changes on the progeny. The report is introduced by a review of previous work on the effects of the administration of anterior lobe hormone on female and male germ cells. The rat was the animal used in Boeters' study. The hormone used was the Zondek preparation made from the urine of pregnant women. It was free from ovarian hormone. Subcutaneous or intraperitoneal injections of this material were given daily. The hormone had no effect on castrated animals. In sexually immature animals it caused increased multiplication and rate of formation of spermatogonia, spermatocytes and spermatids, but it did not cause a precocious development of differentiated spermatozoa. Large doses caused degenerative changes in the germinal cells. The damage was overcome after cessation of administration of the hormone, but sexual maturity was delayed. The interstitial tissue increased in amount only if the tubular cells were injured. In mature and old animals the hormone had no effect. The development of the accessory sex organs of young males was hastened by the hormone. This is due to the action of the specific testicular hormone, which is activated by the pituitary hormone.

O. T. SCHULTZ.

THE EFFECT OF HIGH EXTERNAL TEMPERATURE ON THE TESTIS. J. M. LASOWSKY, Virchows Arch. f. path. Anat. **280**:311, 1931.

Young, sexually mature male white mice were kept for from two to forty-five days in a thermostat maintained constantly at from 32 to 35 C. (89.6 to 95 F.). One of the early effects of the high temperature was the descent of the testes into the scrotum. Microscopic examination of the testes revealed a seasonal difference in the effect of the temperature to which the animals had been subjected. In the fall and winter, degeneration of spermatocytes and spermatids occurred early; these cells appeared less resistant to heat than to roentgen rays, which first affect the spermatogonia. Degeneration was followed by regeneration, which restored the testis to normal even when the animals were kept in the elevated temperature environment. In the spring and summer the high temperature had little or no effect on the testes.

O. T. SCHULTZ.

DISEASE AMONG THE CHINESE AND GEOGRAPHIC PATHOLOGY. E. DORMANNS, Virchows Arch. f. path. Anat. **280**:595, 1931.

As a contribution to geographic pathology, Dormanns presents a running commentary, admittedly based on impressions rather than on rich clinical or anatomic statistical material, on some of the more common diseases encountered during his work in the pathologic institute of Sun-Yatsen University, Canton, China. Carcinoma of the penis and papilloma of the external auditory canal are relatively common among the lower classes. Lack of physical work and exercise for many generations among the middle and higher classes has produced an asthenic type that appears to have a high susceptibility to tuberculosis. The frequency of emphysema and bronchiectasis in the coolie class is ascribed to the use of the shoulder yoke for the bearing and drawing of heavy burdens. A third of 209 primary benign and malignant tumors encountered occurred in women. In organ distribution of malignant tumors, the female genitalia and next the breast were most commonly affected.

O. T. SCHULTZ.

RELATION OF THE SUPRARENALS TO HYPERTENSION AND ARTERIOSCLEROSIS. M. GOLDZIEHER, Virchows Arch. f. path. Anat. **280**:749, 1931.

This is a development, based in part on morphologic evidence, of the author's previously stated thesis that hyperfunction of the suprarenal medulla is an important etiologic factor in hypertension, arteriosclerosis and chronic nephritis. Such hyperfunction need not be associated with hypertrophy of the suprarenals. Hypertrophy is usually due to an increase in cortical tissue. Goldzieher conceives the

cortical hormone to be antagonistic in its action to the medullary hormone. Cortical hypertrophy may therefore be a compensatory process, the aim of which is the overcoming of the hyperactivity of the medulla. In hypertension and arteriosclerosis, observations that help establish the important rôle of suprarenal medullary hyperfunction are marked muscular hypertrophy of the suprarenal veins, higher average total content in epinephrine, even when the suprarenals are normal or subnormal in size, and morphologic similarity of the pheochrome tissue of the gland to that of pheochrome tumors. The diagnosis of hypertension and arteriosclerosis may be deduced from the histologic structure of the suprarenals.

O. T. SCHULTZ.

EFFECT OF LIGATION OF EFFERENT SEMINAL PATH ON SPERMATOGENESIS. A. NEMILOFF, Virchows Arch. f. path. Anat. **280**:776, 1931.

The body of the epididymis was ligated at its middle in dogs, cats, rabbits, guinea-pigs, rats and goats. The behavior of the animals was observed before and after operation. At intervals of from a few hours to many days after ligation the testes were removed and examined histologically. Old and young animals were used. Following recovery from the operation the animals manifested increased sexual desire and activity. Ligation of the epididymis was preferred over ligation or resection of the vas as causing less mechanical or circulatory change in the testis. The author had also for examination tissue from the testes of men who had undergone the Steinach rejuvenation operation. Following ligation spermatogenesis ceased, and the seminal epithelium of the testicular tubules disappeared more or less completely. Study of his material led the author to conclude that the Sertoli cells form a syncytium in which the seminal epithelium is embedded. The syncytium is a colloid the physical states of which may vary from gel to sol. Under normal condition the syncytium is a gel in which the seminal epithelium is held in a fixed position and undergoes the succession of changes characteristic of spermatogenesis and the formation of spermatozoa. After ligation of the epididymis the syncytial gel is transformed into a sol. The mutual spatial relations of the tubular epithelial cell are disturbed, and the incompletely differentiated cells are carried into the lumen of the tubules. Here they degenerate and liquefy. The products of this process are resorbed and constitute the male sex hormone. The interstitial cells of the testis are a reticulo-endothelial tissue that functions in the metabolism of the tubular epithelium.

O. T. SCHULTZ.

CHOLESTEROL METABOLISM OF THE LIVER. G. A. MERKULOW, Virchows Arch. f. path. Anat. **280**:829, 1931.

Remesow, under whose direction the work here reported was done, has maintained that in the liver cholesterol is transformed into glycogen, passing through an intermediate glycocholesterid stage. In the experiments reported, a 5 per cent colloidal suspension of cholesterol in oil was injected directly into the portal vein of full-grown rabbits. The quantity injected was such as to cause the liver to assume a milky appearance. The animals were killed at intervals of from five to sixty minutes after the completion of the injection. Some of the animals died within from forty to fifty minutes in a state of shock, which was held to be hyperglycemic in character, since blood sugar values as high as 372 mg. per hundred cubic centimeters were noted. The internal organs, especially the liver of the experimental and control animals, were examined for lipoid and glycogen. With sudan III stain little or no fat or lipoid could be detected, even in animals that were killed five minutes after the injection of large quantities of cholesterol. In animals that lived from twenty to forty-five minutes, the liver was found, by chemical and histochemical methods, to contain huge quantities of glycogen. The author interprets his experiments as substantiating the claim that cholesterol is quickly transformed into glycogen in the liver.

O. T. SCHULTZ.

Pathologic Anatomy

CHANGES IN THE MIDDLE AND INTERNAL EAR FOLLOWING CHRONIC OTITIS MEDIA. H. BRUNNER, Virchows Arch. f. path. Anat. **281**:352, 1931.

A medicolegal necropsy of a man, aged 30, furnished the material for a histologic study of the end-results of chronic otitis media. When he was 2 years of age, an operation was done on the left ear; a scar posterior to the ear suggested that it was a mastoid operation. The ear continued to discharge until he was 8 years of age. Examination disclosed that the middle ear had been destroyed by the suppurative process and had been replaced by spongy bone and embryonic mucoid tissue. The internal ear also had been destroyed and had been replaced by compact bone. The facial nerve, likewise damaged during the suppurative stage, had regenerated with the formation of a neuroma-like enlargement.

O. T. SCHULTZ.

CONGENITAL CALCIFICATION OF THE ARTERIES AND OTHER TISSUES. W. IFF, Virchows Arch. f. path. Anat. **281**:377, 1931.

A child died a few minutes after its birth during the eighth month of pregnancy. Hydramnion had been present. Necropsy revealed widespread calcification of the inner portion of the media of the large and medium-sized arteries. A lesser degree of calcification was present in the intima and adventitia. Calcium had been deposited also in the interstitial tissue of the thyroid gland and kidney, in the renal glomeruli and glomerular capsules, in the retroperitoneal adipose tissue, in the pia-arachnoid of the brain, in the umbilical vein and in the placenta. In the arteries, the calcium had been deposited in the chromotropic ground substance. The femoral artery contained a larger amount of this substance than the corresponding vessel of a normal new-born infant, but no evidence of disorganization of the ground substance could be detected. Iff believes that dystrophic calcification, calcium metastasis, calcium gout and disturbance of calcium metabolism are to be excluded as causes of the calcification. He ascribes it to incomplete maturation of the connective tissue ground substance, which may have been congenital or the result of hydramnion.

O. T. SCHULTZ.

THE VASCULAR INVOLVEMENT IN ACUTE RHEUMATIC FEVER. F. KLINGE and E. VAUBEL, Virchows Arch. f. path. Anat. **281**:701, 1931.

In three previous papers that have been abstracted in the ARCHIVES, Klinge has described, as the earliest and most characteristic histologic change in acute rheumatic infection, fibrinoid swelling and degeneration that progress to fibrinoid necrosis in the connective tissue of the various organs. This acute reaction is followed by a subacute stage characterized by the formation of focal granulomatous lesions and Aschoff bodies. The granulomatous lesions heal by scar formation. In the present communication, the vascular reactions are described in detail. In the endocardium, in the aorta and the systemic arteries, in the pulmonary arteries and their branches, and in the veins there occurs the same fibrinoid degenerative process noted in other tissues. The acute process may involve the vascular system widely and diffusely or focally. It may be associated with varying degrees of leukocytic and lymphocytic infiltration of the intima and adventitia. Where necrosis leads to destruction of elastic and muscle fibers, focal granulomatous lesions with giant cells develop. The early diffuse or localized degenerative reaction and the later proliferative reaction may heal without leaving a trace or may lead to connective tissue scar formation. The latter process manifests itself as arteriosclerosis indistinguishable from nonspecific arteriosclerosis. Klinge and Vaubel think it probable that many cases of arteriosclerosis of unknown etiology may have had their inception in a rheumatic infection. In the smaller arteries, the cellular infiltrative and proliferative reaction may lead to a histologic picture strikingly like that of periarteritis nodosa. In the aorta and pulmonary artery, the same

reaction may result in lesions like those of syphilis. The differential diagnosis of these conditions is discussed. The differentiation between the vascular involvement in rheumatic infection on the one hand and periarteritis nodosa or syphilitic mesaortitis on the other may at times be impossible on a histologic basis. The article, and apparently the series, ends with a discussion of the etiology and nature of acute rheumatic fever. Whether the infection is due to a specific virus or other living agent, or to a bacterial organism that localizes at a primary focus, or to a bacterial organism that develops specific biologic properties after its localization in the primary focus, cannot be decided at present. It is also impossible, at present, to determine whether the generalized manifestations of the disease are due to the circulation of a living agent or of a toxin or of a protein that elicits reactions of an allergic character.

O. T. SCHULTZ.

CERVICAL THROMBOPHLEBITIS AND SEPSIS SECONDARY TO TONSILLAR INFECTION. A. GREIFENSTEIN, Virchows Arch. f. path. Anat. **281**:748, 1931.

Greifenstein presents a study of four cases of tonsillar and peritonsillar infection that led to thrombophlebitis of the large veins of the neck and fatal sepsis. He compares with these one case of thrombophlebitis and sepsis following otitis media, one following the extraction of a tooth, and two following nasal furuncle. The tonsillar infections led to diffuse phlegmonous lymphangitis of the deep tissues of the neck, and this in turn to phlebitis and thrombosis of the large cervical veins, from which the infecting organisms entered the blood stream. The venous involvement may lead to discrete intimal inflammatory lesions over which multiple discontinuous thrombi form. In the cases of sepsis following otitis media and extraction of a tooth, spread of the infection to the lungs was ascribed to propagation of the thrombophlebitic process into the collaterals of the jugular vein. In the two cases of nasal furuncle, the process was propagated along the vena angularis and vena ophthalmica to the cavernous sinus.

O. T. SCHULTZ.

DIFFERENTIAL HISTOLOGY OF SYPHILITIC AND NONSPECIFIC CHRONIC ENDOCARDITIS OF THE AORTIC VALVE. J. BENEDICT, Virchows Arch. f. path. Anat. **281**:780, 1931.

Syphilis involves the aortic valve by direct continuation of the inflammatory process from the root of the aorta to the valve segments in an ascending or descending course. In the former, the process proceeds upward exclusively on the aortic surface of the segments from the sinus of Valsalva. In descending involvement, the process reaches the valve by way of the commissures, proceeding downward along either the aortic or the ventricular surface of the segments of the valve. The reaction is an inflammatory one. The free margin of the valve may undergo noninflammatory sclerotic thickening as the result of a functional reaction to widening of the root of the aorta. In the early stages, the valve segments are increased in all dimensions through hyperplasia of the interstitial tissue of the valve between the two elastic lamellae; this process is not histologically characteristic of syphilis. In nonspecific chronic endocarditis, the process is localized exclusively on the ventricular surface of the valve. It is the result of thrombotic organization and is most marked at the line of closure. Functional, noninflammatory, sclerotic thickening of the free margin of the segments occurs only in syphilis, but in both syphilitic and nonspecific endocarditis the free margin may undergo inflammatory thickening. In addition to differences in localization, the essential histologic difference between the two forms of chronic endocarditis is seen in the elastic lamellae of the valve. The elastic lamella of the aortic surface is involved only in the ascending form; the endocardial lamella, in both the syphilitic and the nonspecific forms. In syphilis, the elastic tissue is hypertrophied; in nonspecific endocarditis, it is torn and disorganized.

O. T. SCHULTZ.

THE NATURE OF CLOUDY SWELLING. V. UHER, Virchows Arch. f. path. Anat. **281**:821, 1931.

Cloudy swelling is not characterized by an increase in intracellular protein, since quantitative nitrogen determinations revealed no increase, but sometimes a decrease. Potassium ions were found to be decreased, sodium ions increased. Parallel with this alteration went a decrease in chloride and an increase in phosphate. The ninhydrin reaction revealed increased protein cleavage. In parenchymatous degeneration, swelling of intracellular colloids, increased osmotic pressure and altered surface tension lead to increased intake of water by the cells. The altered surface tension causes condensation of protein aggregates at the surface of the cell, a state that manifests itself by clouding. O. T. SCHULTZ.

ANGIOMATOSIS OF THE RETINA (VON HIPPEL AND LINDAU'S DISEASE). G. KNODEL, Virchows Arch. f. path. Anat. **281**:886, 1931.

Knodel presents a case of angiomatosis of the retina, the rare condition described by von Hippel in 1904 after he had had cases under observation for eleven years. In Knodel's patient, retinal abnormality of undetermined character was noted in 1917. In 1926, she began to have recurrent attacks of vomiting. In 1928, there developed symptoms referable to the cerebellum and upper part of the cord. Death followed an attempt at operation on the cerebellum. The retinal lesions, which were multiple, consisted of closely placed vessels of capillary type. The upper part of the cervical cord, the medulla and the pons contained an elongated, poorly defined area of tissue of similar structure. In this were many pseudoxanthomatous cells, previously described in the angiomatous tumors of retina and brain. The tumor in this situation was associated with syringomyelia and diffuse gliosis. A point of interest in Knodel's case is that the patient was the daughter of a man who belonged to the group of patients whose cases were reported in 1904 by von Hippel and in whom the latter had made the diagnosis in 1895. The familial occurrence of the condition and the association of retinal angiomatosis with similar lesions of the brain or cord lend support to the view that the condition has its basis in a congenital maldevelopment. O. T. SCHULTZ.

FATAL RUPTURE OF THE AORTA FROM APPARENTLY MINOR CAUSES. BERTRAM LEVINSON, Virchows Arch. f. path. Anat. **282**:1, 1931.

Several cases are presented to support the thesis that in so-called spontaneous rupture of the aorta there are always minor preexisting inflammatory or degenerative changes, which have previously been overlooked but which can always be found by a study of serial sections at the site of rupture. The beginning of the tear is at the altered area; it extends into normal tissue. Sections taken at random through such normal areas have led previous workers to the erroneous conclusion that rupture of the normal aorta occurs.

In two cases of spontaneous rupture of the ascending aorta there were small areas of suppurative mesaortitis associated with necrosis of the media, at the point of origin of the tear, and in no other place in the aorta. In ninety cases of acute suppurative aortitis reported in the literature there was rupture of the aorta in eighteen. The two reported here are remarkable because of the small area affected.

In two other cases of spontaneous rupture of the ascending aorta there were small areas of a type of mucoid degeneration and necrosis of the media described by Gsell, Erdheim and Cellina. In these, too, the affected areas were surprisingly small.

Two other cases of rupture of the aorta in persons committing suicide who fell from a height presented normal aortas. In such cases, the tear results from purely mechanical causes. The ascending aorta is almost invariably affected, but this does

not imply a previous alteration of the wall of this part. There are several mechanical factors involved, about which there are various theories.

PERRY J. MELNICK.

VALVULAR CHANGES IN SYPHILITIC MESAORTITIS. HARALD KRISCHNER, Virchows Arch. f. path. Anat. **282**:30, 1931.

Thirty-four cases were studied microscopically to decide whether the syphilitic process spreads from the aorta to the valves, or whether the valvular changes are secondary. In all there was obvious aortic insufficiency with thickening of the commissures and of the free margins of the valves. Sections through the commissures showed the syphilitic process extending up to the base of the valves, but not into them. Sections through the middle of the valves failed to show any syphilitic infiltrations, even near the base of the valves. The thickening was nonspecific, composed of an increase of either the collagenous or the elastic tissue of the various layers of the valves or in the form of subendocardial cushions. The valvular insufficiency is therefore the result of the widening of the annulus fibrosus due to the syphilitic mesaortitis, and the valvular thickenings are secondary formations due to mechanical causes. In six of the cases which were combined with acute, subacute or rheumatic endocarditis, the endocardial changes were distinct. There was no evidence of a syphilitic endocarditic process.

PERRY J. MELNICK.

MYOCARDITIS PERNICIOSA. W. S. BOIKAN, Virchows Arch. f. path. Anat. **282**: 46, 1931.

In a 28 year old woman who died of cardiac decompensation following an illness of four months, the heart showed no changes in the endocardium, valves or coronary arteries, but presented the picture of progressive chronic interstitial myocarditis. The condition is clearly distinguishable from all other forms of myocarditis. The etiology is unknown, but the process is probably a selective toxic action on the myocardium by a focal infection. A number of such cases reported in the literature have been falsely labeled syphilitic or tuberculous. The symptomatology is that of progressive decompensation with cardiac hypertrophy and dilatation, of no clearly assignable cause, occurring most usually in young adults from 25 to 40 years of age. The pathologic changes consist of characteristic lesions in the myocardium. The endocardial half of the left ventricle, all of the septum, less of the endocardial half of the right ventricle, and very little of the auricles are sclerosed, with yellow-gray foci in the subepicardial layers. Microscopically there is a nonspecific focal, later confluent myocardial inflammation, which starts subendocardially and spreads in recurrent attacks toward the epicardium. The muscle fibers are well preserved and hypertrophic. The disease is a recurrent progressive one, which becomes clinically manifest only after severe myocardial destruction. Because of its progressive and invariably fatal outcome it has received the name myocarditis perniciosa.

PERRY J. MELNICK.

STUDIES OF EMBOLI IN THE HEART. P. GEIPEL, Virchows Arch. f. path. Anat. **282**:67, 1931.

A number of cases are presented in which emboli arising from thrombi in various locations lodged in unusual places in the heart. In four cases, emboli were caught by the network forming the persistent rudimentary eustachian valve (Chiari). In one case, an embolus was caught by such a network forming the thebesian valve, and in one case, by an aberrant fibrous cord in the left auricle. In four cases, emboli were lodged in patent foramina ovalia. Certain macroscopic and microscopic changes in the emboli are observable, such as compression, change in consistency and composition, knob formation and twisting. They are the resultant

on the one hand, of the original form of the embolus and, on the other, of the shape of the valves and of the foramen ovale, pressure by the walls of the heart, systole and diastole of the chambers, and currents especially in the left auricle. Evidence of such action can be found even on free emboli, especially long ones that take an appreciable length of time to pass through the heart. The blood pressure is also a factor in influencing the fate of emboli, as proved by a case of traumatic rupture of the liver in which emboli of hepatic parenchyma were found molded out for a long distance in the pulmonary artery, with rupture of the wall of the artery in several places.

PERRY J. MELNICK.

A CASE OF RETICULO-ENDOTHELIOSIS. G. WIHMAN, Virchows Arch. f. path. Anat. **282**:181, 1931.

A woman, aged 72 at the time of her death, had been admitted to the hospital seven years previously because of enlargement of the abdomen. At that time the liver was found to be moderately enlarged. The blood picture was normal. In two admissions during the interval, progressive enlargement of the liver was noted. At the final admission, she had marked secondary anemia (red blood cells, 2,400,000; hemoglobin, 33 per cent; white blood cells, 3,100). The antemortem diagnosis was abdominal tumor of unknown origin. Necropsy revealed a greatly enlarged liver, enlargement of the spleen, moderate hypertrophy of the lymph nodes and red hyperplasia of the bone marrow. In these organs and tissues there was found, on microscopic examination, diffuse hyperplasia of the reticulo-endothelial elements. In the liver, the hyperplastic process was associated with marked fibrosis.

O. T. SCHULTZ.

INFECTIOUS RETICULO-ENDOTHELIAL HYPERPLASIA IN A CHILD. H.-U. GUIZETTI, Virchows Arch. f. path. Anat. **282**:194, 1931.

A child, aged 3 months, who had been ill at home for three weeks, was admitted to the hospital with bilateral otitis media. There was leukocytosis of 15,300, with 46 per cent lymphocytes and 9 per cent monocytes, and secondary anemia, with 3,000,000 erythrocytes. Physical examination revealed bilateral bronchopneumonia, and roentgenologic examination, an area of cystic osteitis fibrosa in the right humerus. The disease ran a septic course, with multiple hemorrhages into the skin. Death occurred suddenly on the fifth day after admission, after the development of subcutaneous emphysema of the neck. The essential gross findings at necropsy were: bilateral bronchopneumonia; interstitial emphysema of the lungs, mediastinum and subcutaneous tissue, and emphysema of the pericardium; marked enlargement of the spleen and moderate enlargement of the liver; red hyperplasia of the bone marrow; osteitis fibrosa cystica of the right humerus, and multiple hemorrhages and necroses of the thymus. Microscopic examination revealed the presence of numerous large mononuclear cells in the spleen, liver, lymph nodes, bone marrow, bone and interstitial tissue of the lungs. The hyperplastic cells were derived in part from reticulo-endothelium and in part from histiocytes and fibrocytes. The case is interpreted as a diffuse reactive hyperplasia of the reticulo-endothelial system on an infectious basis.

O. T. SCHULTZ.

CONGENITAL HYDROCEPHALUS. G. POMMER, Virchows Arch. f. path. Anat. **282**: 456, 1931.

Pommer describes in minute detail the findings in the brains of eight infants with congenital hydrocephalus. In four the brain contained Verga's ventricle. In the fifth there was no Verga's ventricle, but a slitlike space, the so-called ventricle of the septum pellucidum. Pommer discusses the theories of the formation of these fifth and sixth ventricles and subscribes to Hochstetter's view. Each of the five brains was the seat of an acute subependymal or diffuse encephalitis. Pommer

next describes two cases of hydrocephalus with absence of the septum pellucidum, in one of which the hyrocephalus was associated with porencephaly. The eighth case was one of hydromicrencephaly with porencephaly, due to congenital syphilis. The porencephaly is ascribed to perivascular hydrops about the syphilitically inflamed vessels. In substantiation of this mode of formation of the spaces about the vessels, Pommer adds two cases of acquired syphilis of the brain with perivascular hydrops.

O. T. SCHULTZ.

XANTHOGRANULOMATOSIS (SO-CALLED SCHÜLLER-CHRISTIAN DISEASE). W. K. JGHENTI, Virchows Arch. f. path. Anat. **282**:585, 1931.

Jghenti reports a case of Schüller-Christian disease and discusses this syndrome in relation to other lipoid infiltrative diseases. He states that an eponymic nomenclature for disease complexes is unscientific, and often unjust. In reiterating the objection of Chester to the application of the names of Schüller and Christian to the disease in question, he notes that Hand in 1893 was the first to report a characteristic instance of the disease. Schüller's report, which appeared in 1915, is the third in the literature, and Christian's, which was published in 1919, is the fourth and records the fifth case also. Chiari, in 1931, collected reports of 22 cases from the literature and added one of his own. The disease is characterized clinically by the triad of multiple defects of the bones of the skull, exophthalmos and diabetes insipidus, and anatomically by a diffuse granulomatous proliferation of large mesenchymal cells that contain cholesterol and its esters. The case here reported was that of a boy aged 3 years and 10 months. The first symptoms, noted seventeen months before death, were exophthalmos, multiple nodular swellings of the scalp, and a peculiar eruption of the skin. Shortly thereafter lameness of the left leg developed. Examination at a later period revealed multiple defects of the bones of the skull and a destructive process in the bony pelvis. Polyuria was not noted at any stage of the disease. The blood had a cholesterol content of 244 mg. and 218 mg. two months and one month before death. A hemolytic streptococcus was cultivated from blood taken at necropsy. The granulomatous tissue was most widespread in its distribution. Macroscopically, it was both diffuse and nodular, and was evident in the skin and subcutaneous fat, the bones of the skull and pelvis, the meninges, the lymphoid tissues of the lower part of the small intestine and of the large intestine, the lymph nodes, the lungs, the spleen and the liver. Microscopic examination revealed the presence of similar tissue in most of the other organs. The tissue consisted of large cells, many of which were multinucleated, embedded in a fibrocytic groundwork infiltrated by lymphocytes and plasma cells. The tissue contained areas of hemorrhage and necrosis. The cytoplasm of the large cells varied from finely granular to finely vacuolated. The vacuolated cells, on microchemical examination, contained neutral fats, lecithin and cholesterol, the latter predominating. The infiltrating cells were derived chiefly from the reticuloendothelial system, but were also in part hematogenous. The case differed from others in the greater involvement of the skin and in the presence of xanthogranulomatous lesions in the tongue and in the mucosa of the intestine. In the age of the patient and in the presence of lecithin in the cells, it resembled Niemann-Pick disease (lipoid histiocytosis), but differed in the more marked inflammatory character of the tissue and in the presence of cholesterol in the cells. There is a brief discussion of the other two lipoid infiltrative diseases: Gaucher's disease, characterized by the presence of the cerebroside or galactoside, kerasin; and Niemann-Pick disease, characterized by the presence of the phosphatid, lecithin.

O. T. SCHULTZ.

A CASE OF ALEUKEMIC RETICULO-ENDOTHELIOSIS WITH LIPOID STORAGE. L. J. ERBER, Virchows Arch. f. path. Anat. **282**:621, 1931.

In a man, aged 79, examination revealed moderate enlargement of the superficial lymph nodes. The blood picture was normal at this time. While he was

under treatment, progressive enlargement of the lymph nodes was noted. Death was the result of a wound infection of the hand. The leukocyte count shortly before death was 2,200, with 33 per cent granulocytes, 26 per cent lymphocytes, 3 per cent monocytes and 38 per cent unusually large mononuclear cells. Histologic examination of the lymph nodes revealed replacement of the lymphoid cells by large cells the origin of which could be traced to the reticulum and sinus endothelium. Similar cells in smaller numbers were present in the liver and spleen. The cells were vacuolated and contained neutral fats. The reticulo-endothelial hyperplasia is not believed to have had any relation to the terminal infection. The case is considered unusual and is placed tentatively in the group of reticulo-endothelial hyperplasias with lipoid storage.

O. T. SCHULTZ.

LIPOMATOSIS OF THE PANCREAS IN A CHILD. W. HANTELMANN, Virchows Arch. f. path. Anat. **282**:630, 1931.

A boy, aged 9, died of general amyloidosis due to cervical lymphogranulomatosis. He was not obese, and there was no sugar in the urine. At necropsy, the pancreas was found to be enlarged, owing to adipose tissue, which had replaced much of the acinar tissue. The islets had persisted unchanged. Although fatty infiltration of the pancreas is common in adult obese persons, especially those with diabetes, Hantelmann could find only three previously reported cases of a similar condition in children. In none was there obesity, diabetes or detectable disturbance of function due to loss of the external secretion of the pancreas. He ascribes the replacement of pancreatic tissue by fat in this case to a slowly progressing inflammatory process.

O. T. SCHULTZ.

HISTOLOGY AND FUNCTION OF THE DIAPHRAGM. A. L. STRUKOW, Virchows Arch. f. path. Anat. **282**:643, 1931.

Systematic histologic examination of the diaphragm revealed frequent occurrence of degenerative and secondary inflammatory changes associated with a wide variety of diseases in all age groups. Alterations are especially marked in circulatory disturbances and uremia. Fatty change of the muscle fibers, which was frequently seen, is the result of preceding degenerative changes and bears a direct relation to the degree of such alterations and to the severity and duration of the disease. In persons without cardiac or pulmonary lesions, the size of the muscle fibers is equal in the two halves of the diaphragm. Pericardial adhesion and compensated hypertrophy of the heart due to a cardiac lesion or pulmonary emphysema cause hypertrophy of the diaphragmatic muscle fibers. Decompensated cardiac lesions lead to passive congestion and to degenerative, atrophic and secondary inflammatory changes that are more marked in the left than in the right side of the diaphragm, from which Strukow concludes that under such conditions the right side is more active than the left. Lesions of the respiratory system, if unaccompanied by cardiac hypertrophy, lead to little or no muscular hypertrophy of the diaphragm. The association of muscular hypertrophy with cardiac lesions but not with respiratory disease indicates that the diaphragm, and especially its right half, exerts an important compensatory function in diseases of the heart. Wasting diseases cause only slight atrophy of the diaphragm. Diaphragmatic pleuritis or peritonitis involves the deeper tissues of the diaphragm and leads to changes in its musculature.

O. T. SCHULTZ.

CALCAREOUS CONCRETIONS OF THE BRAIN. B. G. SCHIELE, Virchows Arch. f. path. Anat. **282**:790, 1931.

Calcareous concretions in the brain, associated with calcification of the intracerebral vessels, have been described by a number of investigators, the condition having been noted usually in isolated cases of various psychotic diseases. Ostertag, in a systematic examination of one hundred brains of persons of various ages with and without psychotic manifestations, found that the concretions might be

present in the brains of persons who had never exhibited abnormal psychic or cerebral symptoms. He believed them to be the result of disturbed metabolism of the tissues of the central nervous system and, in agreement with previous observers, found that the concretions were composed primarily of precipitated protein material, which became secondarily calcified. Schiele reports a case because of the unusually marked degree of the process and because the brain was carefully studied in both the fresh and fixed states. The patient was 55 years old at the time of death, and in the later years of his life had had a number of epileptiform seizures with progressive psychic disturbance. Histochemical and quantitative chemical examinations revealed an extraordinary quantity of calcium in the brain, 9.23 per cent, as compared with 0.03 and 0.01 per cent in two control cases. The calcium content of the ash of brain tissue was 36.32 per cent, as compared with 2.17 and 1.11 per cent in the controls. The concretions were chiefly about the blood vessels, but occurred also in the interstitial tissue. The blood vessels were markedly calcified, the process being even more extreme in the smallest arterioles and capillaries than in larger vessels. The concretions result from the precipitation of colloidal protein material in the perivascular lymph spaces. The protein material is formed by abnormal metabolism of brain tissue, in diseases of the brain itself and in states due to disturbed endocrine function. By adsorption, the concretions become secondarily calcified. Their presence in the perivascular lymph channels interferes with the normal lymph flow, which in its turn alters the metabolism of the tissues. Because of their proximity to the walls of blood vessels, they also cause degenerative changes and calcification of these vessels. The vascular involvement resulting from the presence of the concretions must be sharply distinguished from that of arteriosclerosis.

O. T. Schultz.

Pseudotuberculous Necroses of the Human Liver. H. Schwarz, Virchows Arch. f. path. Anat. **282**:862, 1931.

This article is chiefly a protest against the use of the word pseudotuberculosis for conditions in which there are circumscribed, miliary or larger, tubercle-like, coagulation necroses of the liver, unless the lesions are due to the organism described by Pfeiffer as Bact. pseudotuberculosis-rodentium. Schwarz divides the necroses under discussion into three groups: (1) true human pseudotuberculosis, caused by the Pfeiffer organism; (2) hepatic necroses caused by various other bacteria, and (3) hepatic necroses of unknown origin. He subdivides the second group into: (*a*) those due to organisms culturally like the rodent pseudotuberculosis organism but gram-positive, which he terms Bact. pseudotuberculosis-humanis; (*b*) those due to other species of bacteria obtained on culture; (*c*) those due to unindentified bacteria that were not grown, and (*d*) those due to argentophil bacteria that could be stained in the tissues by the Levaditi procedure but could not be cultivated. He tabulates twenty-seven cases, including two of his own, and places five in group 1, five in *2a*, two in *2b*, six in *2c*, three in *2d* and six in 3. Nowhere in the article is there any mention of possible relations of the Pfeiffer organism of rodent pseudotuberculosis to the paratyphoid B and B. aertrycke groups.

O. T. Schultz.

Microbiology and Parasitology

Further Studies on B. Pseudotuberculosis. H. A. Reimann, Am. J. Hyg. **16**:206, 1932.

The studies indicate that Pasteurella pseudotuberculosis and Past. tularensis are closely related. From the reports of others it also appears that these varieties, together with Past. pestis, belong to one group of bacteria—the Pasteurella group. It is desirable to abandon the term "pseudotuberculosis" for all conditions except that associated with Past. pseudotuberculosis-rodentium of Pfeiffer. Even in this case, the term is not satisfactory.

Author's Summary.

VACCINIAL INFECTION OF THE CHORIO-ALLANTOIC MEMBRANE OF THE CHICK EMBRYO. E. W. GOODPASTURE, A. M. WOODRUFF and G. J. BUDDINGH, Am. J. Path. **8**:271, 1932.

Vaccinial lesions of the chorio-allantoic membrane of chick embryos are described. Guarnieri bodies have been demonstrated for the first time in mesodermal cells (endothelium and fibroblasts). Evidence has been presented that the Guarnieri bodies are composed in part of Paschen corpuscles. Similarities between Borrell corpuscles (fowl-pox), Lipschütz corpuscles (molluscum contagiosum) and Paschen corpuscles (vaccinia) are pointed out. It is suggested, on the basis of the cytology of the lesions, that the virus of molluscum contagiosum would require a culture of ectodermal epithelium to initate its growth outside the body; fowl-pox would require either ectodermal or entodermal epithelium, while vaccinia would multiply in a culture of cells from any of the three germinal layers.

AUTHORS' SUMMARY.

MICROCOCCUS PHARYNGIS SICCUS ENDOCARDITIS. I. GRAEF, C. E. DE LA CHAPELLE, and M. C. VANCE, Am. J. Path. **8**:347, 1932.

Bacterial endocarditis (malignant) caused by Micrococcus pharyngis-siccus is presented in a human subject with preexisting valvular disease of rheumatic origin.

AUTHORS' SUMMARY.

INVASION OF THE WALL OF THE INTESTINE BY TRICHOMONAS HOMINIS. KENNETH M. LYNCH, Am. J. Trop. Med. **12**:247, 1932.

The question of the effects, if any, on the host of Trichomonas hominis in the intestine is still a subject of debate. Lynch secured the transverse colon from a patient just dead from peritonitis due to rupture of the colon. During life the patient had had enormous numbers of active trichomonads in the stools. There were many flagellates of about half the ordinary size and there were many large forms in a state of division. In the stool were, also, numerous leukocytes, red blood corpuscles and blastocysts. Microscopically, the mucosa of the colon was necrotic, with diffuse inflammation and fibroblastic proliferation, hemorrhage and edema below. In the necrotic lining were scattered trichomonads. In the submucosa below the necrosis, where leukocytosis was prominent, scattered trichomonads and occasionally a group or colony occurred in the intercellular spaces. Where necrotic sinuses penetrated the inner musculature, flagellates infiltrated the margins and extended into the muscle. The trichomonads might easily be mistaken for amebas. It was not until the trichomonads came into direct contact with the muscular coat by the extension of the necrosis that they found a favorable avenue for migration.

S. N. MENDELSOHN.

A VIRUS DISEASE OF PARROTS AND PARRAKEETS DIFFERING FROM PSITTACOSIS. T. M. RIVERS and F. F. SCHWENTKER, J. Exper. Med. **55**:911, 1932.

The virus of parrots and parrakeets discovered by Pacheco, Bier and Meyer is unrelated to the agent causing psittacosis either in birds or in man. The virus is fairly species-specific and manifests itself chiefly by the production of areas of focal necrosis in the liver and acidophilic intranuclear inclusions in affected cells.

AUTHORS' SUMMARY.

VIBRIOS FROM THE INTESTINAL TRACT OF THE GRAY RAT. F. S. JONES, R. B. LITTLE and M. ORCUTT, J. Exper. Med. **55**:939, 1932.

The vibrio obtained is a normal inhabitant of the lower part of the ileum and cecum and may be cultivated from these regions. While in character of growth and morphology it is like that found in an intestinal disease of cattle, it differs serologically from the bovine organism.

AUTHORS' SUMMARY.

VIRULENCE OF PNEUMOCOCCI. L. D. FELTON, J. Exper. Med. **56**:13 and 27, 1932.

In a study of different tissue extracts as mediums for the growth of pneumococci, used in an automatic transfer device, the following observations were made: Mediums made from calf lung or heart, or from horse skeletal muscle, maintained virulence over a long period of time. Those made from calf spleen led to a decrease in virulence. Lung medium caused an increase in virulence of seven strains of pneumococci. Virulence was maintained in normal horse serum, but rapidly decreased in immune serum or in pneumococcic antibody solution, a finding that confirms the work of Stryker. Immune serum freed from protective antibody gave results similar to normal serum. Medium made from the entire rabbit appeared less suitable for the maintenance of virulence than that made from the entire guinea-pig.

The growth of a virulent pneumococcus of type I in an automatic transfer device on a medium that aerobically maintained virulence resulted in a decrease in the presence of pure oxygen or pure carbon dioxide, but in no change in the presence of nitrogen. Partial pressure of oxygen—that is, 5 parts with 95 parts nitrogen by volume, and 10 parts with 90 parts nitrogen—resulted in a decrease in virulence, whereas with 20 parts oxygen and 80 parts nitrogen the decrease was almost negligible. Mediums which aerobically failed to furnish suitable constituents for maintenance of virulence—that is, spleen, aminoid peptone, powdered milk, beef infusion, whole rabbit and rabbit muscle—also failed under nitrogen. Mediums from whole guinea-pig kept the organism virulent for 246 transfers under nitrogen, but with some decrease. Mediums made from discarded mice, survivors of pneumococcic infection, furnished conditions under nitrogen which caused first a decrease of virulence, but later, after 246 transfers, a restoration to a more virulent state. Gradual increase in temperature over a period of ten days from 36.5 to 42 C. in a sample of medium which was otherwise suitable for maintenance of virulence under aerobic conditions resulted in a decrease in virulence.

AUTHOR'S SUMMARIES.

CELLULAR REACTIONS IN THE MENINGES OF RABBITS TO TUBERCULO-LIPOID, PROTEIN, AND POLYSACCHARIDE, COMPARED WITH THE EFFECTS OF TUBERCLE BACILLI. J. VAN ALLEN BICKFORD, J. Exper. Med. **56**:39, 1932.

Both living and dead tubercle bacilli, as well as tuberculophosphatide, give rise to lesions in which the same type of cell is found, a cell that may prove characteristic of the meningeal reaction. After the administration of phosphatide, this cell is produced by the phagocytosis of lipoid material. The vacuoles of these cells are slowly broken into smaller and smaller size until they correspond to the type found in the epithelioid cells with coarse vacuoles. This change is much slower in the cells of the meninges than in the cells of the omentum and subcutaneous tissue. Intrathecal injections of tuberculoprotein produce a characteristic rise in temperature in normal and tuberculous rabbits. Both normal and tuberculous rabbits, after repeated intrameningeal injections of a given dose of tuberculoprotein, may fail to give a rise in temperature and later react to a larger dose.

AUTHOR'S SUMMARY.

TYPHUS RICKETTSIAE. H. PINKERTON and G. M. HASS, J. Exper. Med. **56**:131 and 145, 1932.

In tissue cultures at 32 C., typhus rickettsiae increase rapidly within the cytoplasm of infected cells and by the fourteenth day have infected practically every cell. There is no loss of virulence during the successful culture of infected cells. Rickettsiae are not seen within the nuclei.

Temperatures higher than 32 C. have a detrimental effect on the intracellular multiplication of typhus rickettsiae, owing to the stimulation of their defense mechanism.

SPOTTED FEVER RICKETTSIAE. H. PINKERTON and G. M. HASS, J. Exper. Med. **56**:151, 1932.

On cultivation of spotted fever rickettsiae in tissue cultures at 32 C., the rickettsiae multiply extensively in the nuclei of the cells, where they form spherical clusters of various sizes.

EFFECT OF LYMPHOCYTOSIS FROM CHICK EMBRYO EXTRACT ON TUBERCULOSIS IN RABBITS. K. C. SMITHBURN, J. Exper. Med. **56**:173, 1932.

Chick embryo extract given intravenously did not favorably influence the course of experimental tuberculosis in rabbits, although it caused lymphocytosis and lymphoid hyperplasia. The treated animals showed lower values for hemoglobin and red blood cells than the controls inoculated from the same suspension of tubercle bacilli. The increase in the number of young, immature cells in the lymph nodes was accompanied by more extensive tuberculous lesions in the lymph nodes and especially in the germinal centers of the nodes. A possible analogy to lymphatic tuberculosis in children is suggested. The observations of previous investigators on the progression and later regression of lesions in experimental tuberculosis have been confirmed. The distribution, character and extent of the lesions have been studied and are presented in tubular form.

AUTHOR'S SUMMARY.

DIPHASIC NATURE OF BOVINE TUBERCULOSIS IN RABBITS. R. M. THOMAS, J. Exper. Med. **56**:185, 1932.

In a large group of rabbits inoculated intravenously with bovine tubercle bacilli, the disease resolved itself into two distinct phases. The first phase was manifested in widespread diffuse lesions, which subsequently regressed. The mortality showed a rise and fall during this period, correlated with the extent of the lesions and with the changes in the blood cells. The duration of this phase was approximately from eighty to ninety days. The mortality again rose and fell during a period when all animals showed lesions of a chronic nature. The number of fatalities in the first phase was a function of the size of the dose. When the size of the dose and other conditions were held constant, a definite basis on which to compare the reactions of treated animals was established. In the first phase, the changes in the blood cells reflected the course of the lesions when other signs were lacking, and offered a valuable means of making an estimate of the state of resistance of the animal from time to time. Blood counts made on rabbits before their inoculation with tuberculosis were analyzed with regard to the relative longevity of the animals; it was found that the animals in which the blood cells of the various sorts deviated least from the modal value for the entire group survived longer than those the counts for which were significantly high or low.

AUTHOR'S SUMMARY.

PRIMITIVE OR FILTRABLE FORMS OF BACTERIA AND THEIR OCCURRENCE IN ASEPTIC MILK. H. J. BRUECKNER and J. M. SHERMAN, J. Infect. Dis. **51**: 1, 1932.

Primitive forms of bacteria were present in the aseptically drawn milk of a majority of the healthy cows studied. The method used for the detection and quantitative estimation of these bacterial forms was to make serial dilutions of the milk in dextrose beef infusion broth and to incubate the dilution cultures for one day at 37 C. and then at 30 C. for about two weeks. After incubation, the broth cultures from the higher dilutions, which showed no growth of ordinary bacteria, were seeded on the surface of dextrose beef infusion agar. After incubation at 37 C. for two days, the plates were examined for the presence of definite, minute colonies. Growths were verified by the finding of definite bacterial cells in stained preparations. The results, as well as other work in this laboratory, indicate that

primitive forms of bacteria may sometimes occur in numbers approximating a trillion (10^{12}) per gram of substance. Cocci and small rods were observed. While the theory of a life cycle advanced by previous investigators is a plausible and attractive explanation of the results, the work reported here does not answer the question whether these organisms are definite species or represent only dissociative forms or cyclostages in the development of ordinary bacteria.

AUTHORS' SUMMARY.

RELATIONSHIP OF BACTERIOPHAGE TO DISEASES OF LABORATORY ANIMALS. M. G. COLVIN, J. Infect. Dis. **51**:17, 1932.

From a review of the results of bacteriophage therapy in natural and experimental diseases of laboratory animals it appears that there have been no therapeutic successes since the early experiments of d'Herelle with fowl typhoid. Attempts to adapt bacteriophage to acting in serum have been partially successful, but have not given it therapeutic value. Streptococcic lymphadenitis of guinea-pigs is described. A bacteriophage of maximum virulence against the etiologic organism was used in attempts to modify the course of the disease, with little or no success. The treatment gave evidence that it was not entirely harmless. A degree of immunity obtained in guinea-pigs after their recovery from the abscesses of streptococcic lymphadenitis. It appears that, within the tissues, the conditions are such as to inhibit the action of a bacteriophage that is thoroughly effective in vitro.

AUTHOR'S SUMMARY.

INHERITANCE OF RESISTANCE AND SUSCEPTIBILITY TO INFECTIOUS ABORTION. M. MANRESA, J. Infect. Dis. **51**:30, 1932.

Predispositions toward susceptibility and resistance to infectious abortion are definite characteristics of each strain or family of rabbits. These characteristics are transmitted by inheritance to successive generations, probably through a single pair of mendelian factors. The characteristic for resistance is dominant over that for susceptibility. Whether this dominance is complete or partial is a matter for future study. An appreciable amount of immunity is developed in susceptible dogs following artificial inoculations with a virulent strain of Brucella abortus. The immunity is transitory.

AUTHOR'S SUMMARY.

METABOLISM STUDIES ON THE BRUCELLA GROUP. K. F. MEYER and C. E. ZOBELL, J. Infect. Dis. **51**:72, 91, 99 and 109, 1932.

Bacteriostatic Action of Dyes (p. 72).—The factors that invalidate the accuracy of the dye plate test devised by Huddleson are discussed. The advantages of a semisolid medium in tubes, with a low protein content and a constant concentration of dye, inoculated with a definite number of cells of Brucella, have been demonstrated experimentally. With this method, the fundamental differences of the various strains of Brucella have been duplicated with an accuracy of 98 per cent. According to their tolerance toward thionine, fuchsin and pyronine, 444 cultures obtained from 20 countries have been tentatively classed into 3 general groups. There is a tendency for the boundaries of the groups to merge into each other (owing to gradations). Atypical porcine strains and closely related types have been encountered in a series of 37 Danish cultures. Thionine-tolerant bovine abortus strains resembling the melitensis types occur in central Europe. Three strains from caprine milk, recently isolated on the island of Malta, are indistinguishable serologically and according to the dye and other tests from the bovine abortus types. A Swiss porcine culture reacts like Br. abortus. Five American caprine strains, isolated from the blood, milk and other tissues, behave like melitensis types.

Production of Hydrogen Sulphide (p. 91).—The ability of representatives of Brucella to produce hydrogen sulphide, as a single differential test, is of little value, even when the test is conducted under controlled conditions of inoculation and incubation. Melitensis strains are active producers of hydrogen sulphide when

the oxidation-reduction potential of the culture medium is adjusted by exclusion of oxygen or by the addition of reducing substances. In conjunction with the dye tolerance tests, the ability to produce hydrogen sulphide subclassifies the Brucella group into 3 major and 3 minor subgroups. Cultures that react in the dye tests like the melitensis type, but that generate hydrogen sulphide on liver agar slants, may consist of a melitensis and an abortus variant. Primary blood and tissue cultures must be thoroughly studied with respect to the types of colonies before they are subjected to the identification tests.

Nitrate and Nitrite Reduction (p. 99).—The representatives of Brucella reduce nitrates to nitrites when tested in semisolid mediums containing 0.2 per cent potassium nitrate. The nitrites are also rapidly reduced. The abortus and suis types exhibit pseudo-anaerobic growth throughout the nitrate medium, while the melitensis strains grow in a zone a few millimeters below the surface. The suis strains destroy 0.05 per cent potassium nitrite in five days, while the abortus and melitensis types lack this ability. The melitensis varieties are in general more active reducers of nitrites than the abortus. In mediums containing 0.2 per cent each of potassium nitrate and potassium iodide, the suis types evolve an abundance of nitrogen gas with a rapid disappearance of nitrates and nitrites, while the abortus types rarely liberate gas under identical conditions. The melitensis and the Danish porcine strains, which exhibit no pseudo-anaerobic growth, although capable of destroying 0.002 per cent potassum nitrite, fail to generate gas. When judiciously employed, these differences in the nitrate and nitrite metabolism may be used in the characterization of the representatives of Brucella. The use of a semisolid nitrate medium for the nitrate-reduction test as a standard procedure is advocated.

Dextrose Utilization (p. 109).—Quantitative determinations in duplicate with two methods on 33 abortus, 21 melitensis and 19 suis strains of Brucella failed to demonstrate any appreciable difference in their dextrose utilization. The modified ferricyanide method of Schmidt for estimating reducing sugars in bacterial substrata gave more uniform results than the copper reduction method of Somogyi. In bacterial substrata containing small amounts of dextrose, neither method was found to be sufficiently delicate to detect differences of less than ± 3 per cent of the remaining sugar. In mediums that contained 1 and 5 per cent peptone, the average dextrose utilization of the abortus types was less than that of the other types, but the difference was not great or constant enough to be of differential significance. Determinations of the terminal reactions (p_H) on 286 strains in dextrose mediums failed to distinguish between the types of Brucella. Nitrates accelerated the consumption of dextrose by Brucella.

AUTHORS' SUMMARIES.

FILTRABILITY OF PURE CULTURES OF THE TUBERCLE GROUP OF MICRO-ORGANISMS. R. R. MELLON and L. W. FISHER, J. Infect. Dis. **51**:117, 1932.

A bacillus, somewhat variable in its acid-fastness, was studied six years ago under conditions under which it developed nonacid-fast granules (Much), which were filtered through a Berkefeld N filter. These underwent slow and capricious germination to a nonacid-fast diphtheroid organism with cultural characteristics quite in contrast with the original. During the interim a seasonal dissociation, spontaneous in character, recurred in the spring of the year in four of six years during which the strain was under observation. Such periodicity was described by De Vries with the higher plants. More recently, in addition to the diphtheroid form, the original cultural form of the organism was recovered from the filtrates. This appeared to have been induced by a more complete "maturation" of the same gonidial granules that yielded only the diphtheroid if imperfectly matured. Similar results have been observed with bovine and avian strains of tubercle bacilli as far as the isolation of the nonacid-fast forms from the filtrates is concerned. These forms seem to take origin from the granules of Much, thus correlating these classic forms with the nonacid-fast variants that have been described as originating from tubercle cultures. We isolated almost identical strains with

acid-fast granules from such diseases as Hodgkin's disease, benign lymphogranulomatosis (Schaumann) and Boeck's sarcoid, making it seem probable that their in vivo origin may also be from the tubercle bacillus. No opinion can at present be vouchsafed in respect to their rôle in the pathogenesis of these diseases.

AUTHORS' SUMMARY.

ENDEMIC TYPHUS FEVER OF THE UNITED STATES. R. E. DYER, E. T. CEDER, A. RUMREICH and L. F. BADGER, J. Infect. Dis. **51**:137, 1932.

The rat flea (Xenopsylla cheopis) as a vector of endemic typhus meets the requirements of the epidemiologic evidence. The virus of endemic typhus has been recovered repeatedly from rat fleas taken at foci of typhus, and experimental transmission of the virus from rat to rat by means of rat fleas has been carried out in the laboratory. This points to the rat flea (Xenopsylla cheopis) as a common vector of endemic typhus from rat to rat and from rat to man. Rodents may be an important reservoir of typhus in parts of the world where epidemics of typhus occur, and it seems a reasonable hypothesis that epidemics of louse-borne typhus may have their origin from typhus transmitted from rat to man by rat fleas.

AUTHORS' SUMMARY.

FORMOL DETOXICATION OF PURIFIED STAPHYLOCOCCAL TOXIN. F. M. BURNET and M. FREEMAN, J. Path. & Bact. **35**:477, 1932.

Staphylococcic toxin can be readily concentrated by precipitation with acetic acid to give stable preparations. A study of the detoxication of purified toxin has shown that within fairly wide limits the rate of detoxication is proportional to the concentration of formaldehyde used, varies with the square root of the concentration of hydroxyl ions present and possesses a high temperature coefficient. In slowly detoxicated preparations, particularly at alkaline reactions, an intermediate product accumulates which possesses a slower type of hemolytic activity, has no acute killing power, retains most of its skin necrosing power and can be reconverted into typical toxin if the formaldehyde is removed. The changes in binding power induced by formaldehyde treatment do not run parallel to the detoxication. The slower the detoxication, the less the binding power is reduced. The bearing of these observations on the problem of the unity or diversity of staphylococcic toxins is discussed.

AUTHORS' SUMMARY.

MALIGNANT LYMPHOGRANULOMATOSIS AND TUBERCULOSIS. F. BOZANÇON, WEISMANN-NETTER, OUMANSKY and DELARUE, Presse méd. **40**:693, 1932.

Biopsy and necropsy material from six patients with typical lymphogranulomatosis was studied. In addition to histologic procedures and inoculation tuberculin tests were employed in order to disclose a possible relationship between the tubercle bacillus and lymphogranulomatosis. Their conclusions follow: In a large number of cases, lymphogranulomatosis runs a course in which the acid-fast bacillus cannot be incriminated. In instances in which clinical and laboratory methods elicit the association of tuberculosis and lymphogranulomatosis, it is not possible to attribute the genesis of the latter to the tubercle bacillus. Only reproduction of typical lymphogranulomatosis by means of a pure culture of tubercle bacilli would be proof of such a relationship.

B. M. FRIED.

THE VIRUS OF INGUINAL LYMPHOGRANULOMATOSIS. LEVADITI, Med. Klin. **28**: 351, 1932.

The results of new experiments support the view that this disease is caused by a filtrable virus of variable virulence. It responds to electrophoresis in much the same way as the viruses of herpes and encephalitis. Of the animals commonly used for experimental purposes, only the monkey is susceptible. Intracranial inoculations cause meningeal symptoms; inguinal and preputial inoculations, bilateral inguinal

lymphadenitis. The virus is distributed widely in the organs of inoculated monkeys. The virus appears to be antigenic, calling forth virucidal principles in the course of the human disease.

EXPERIMENTAL TUBERCULOUS INFECTION IN TISSUE CULTURE. E. M. WERMEL, Virchows Arch. f. path. Anat. **281**:297, 1931.

When cultures of adult guinea-pig spleen, prepared according to the method of Maximow, were infected with living tubercle bacilli, the latter were phagocytosed by histiocytes and polymorphonuclear leukocytes. The leukocytes and some of the histiocytes that had taken up bacilli died. When a histiocyte was able to overcome the engulfed bacilli and maintain its existence, the bacilli were clumped together, surrounded by a vacuole, and transformed into a yellowish-brown to dark brown pigment. Epithelioid cells and giant cells, both of which were readily formed in the tissue cultures as a reaction to the infection, were not specific types of cells, but enlarged macrophages. In Wermel's experiments, a continuing infection of the tissue culture could not be induced. Either the bacilli overcame the tissue culture and it died, or the tissue culture overcame the bacilli and the latter were killed.

O. T. SCHULTZ.

GIANT CELLS IN THE TONSILS IN MEASLES. W. FINKELDEY, Virchows Arch. f. path. Anat. **281**:323, 1931.

In a child, tonsillectomy was done three days before the appearance of the eruption of measles, and therefore during the period of incubation of the disease. The tonsils revealed catarrhal inflammation of the crypts and hypertrophy and cellular hyperplasia of the reaction centers. In the centers were large numbers of giant cells of a type not previously seen in the tonsil by Finkeldey. Each cell contained numerous nuclei, as many as a hundred or more in a single optical plane. The nuclei were heaped together at the center of the cell. Pyknosis and chromatolysis of nuclei and degeneration and fragmentation of the giant cells were evident. Finkeldey suggests that the reaction within the crypts was due to the infecting virus or agent, and that the hyperplasia of the centers with the formation of giant cells was the reaction to a toxin, and further that the formation of giant cells may have been an allergic phenomenon. [See Warthin, A. S.: Occurrence of Numerous Large Giant Cells in the Tonsils and Pharyngeal Mucosa in the Prodromal Stage of Measles, ARCH. PATH. **11**:864, 1932.]

O. T. SCHULTZ.

ACTINOMYCOSIS OF THE BRAIN. W. N. RUSSKICH and E. S. KRYLOWA, Virchows Arch. f. path. Anat. **281**:796, 1931.

A case of actinomycosis limited to the brain, occurred in a woman, aged 23, the portal of entry having been, it is believed, the eyelid.

O. T. SCHULTZ.

EXPERIMENTAL TUBERCULOTOXIC LESIONS OF THE LIVER. H. GUILLERY, Virchows Arch. f. path. Anat. **281**:801, 1931.

Capsules impervious to tubercle bacilli and filled with a suspension of living bacilli of the human type were implanted in the peritoneal cavities of twelve rabbits. The animals were killed at the end of nine months. In one animal, active tuberculous infection developed from the implant. The remaining animals revealed no gross changes except slight foreign body reaction about the implanted capsule. Macroscopic focal necrosis of the liver, such as had been observed in previous experiments, were not seen. Microscopic examination of the liver, however, revealed cellular granulomatous lesions in the periportal tissue. The reaction, ascribed to a distant action of tuberculotoxic substances, was the same as that caused by the injection of substances extracted from the bodies of tubercle bacilli. It was also similar to the reaction seen in phlyctenular conjunctivitis and in scrofuloderms and sarcoid of the skin.

O. T. SCHULTZ.

PNEUMONOCONIOSIS AND TUBERCULOSIS. M. M. SCHEININ, Virchows Arch. f. path. Anat. **283**:122, 1932.

To what extent pneumonoconiosis predisposes to tuberculosis or influences the course of the latter has received much discussion in the literature. Some have maintained that the combination of the two processes is a disease of its own kind, in which the tuberculous element runs a different and more benign course than in the nonfibrotic lung. Scheinin subjected 188 employees of a porcelain factory to a combined physical, laboratory and roentgenologic examination in 1926 and again in 1929. Of the original group, 73 had given up their work; 8 had died; 15 were incapable of work, and the remaining 50 had left the industry because of progressive poor general health. Of the original group, 3 were considered well at the time of the first examination; 39 had such slight involvement of the lung that they were considered "practically well"; 44 had pneumonoconiosis alone, and the remaining 102 had tuberculosis and pneumonoconiosis. The author believes it fair to take it for granted that the employes were free from pneumonoconiosis when they entered the industry, and that they probably either had latent tuberculosis or were entirely free from this disease. The author concludes that the combination of pneumonoconiosis and tuberculosis is not a disease *sui generis,* but a stage in the development and natural history of the dust lung. The pneumonoconiotic process predisposes to tuberculous infection, the latter arising either from a previously quiescent endogenous focus or from an exogenous source. The degree of fibrosis that results from the combination of the two processes may be dependent on constitutional factors, which may manifest themselves in the degree of phagocytic activity of the macrophages within the lung or in a variable tendency to fibrosis.

O. T. SCHULTZ.

VIRULENCE OF TUBERCLE BACILLI. R. DOERR and E. GOLD, Ztschr. f. Immunitätsforsch. u. exper. Therap. **74**:7, 1932.

Doerr and Gold undertook to reexamine the question of whether the guinea-pig can be infected with a single tubercle bacillus, using an optical method for the separation of one organism and employing five different strains of bacilli, human and bovine. Only three of the twenty-eight animals so infected acquired the disease. The authors conclude that one bacillus is sufficient for the production of tuberculosis in the guinea-pig, and that the failures were due to injections of dead or weakened bacilli. Even a slight increase in the number of bacilli injected swelled the percentage of positive results. The resistance of the animal played a less important rôle; its influence manifested itself mainly with regard to the course of the disease. The authors take a stand against the term "virulence." It is a synthetic artefact created to express two qualities of pathogenic bacteria: infectiousness and pathogenicity. The former may be present without the second in so-called latent infections.

I. DAVIDSOHN.

DIAGNOSTIC VALUE OF BLOOD CULTURE IN EXPERIMENTAL TUBERCULOSIS OF THE RABBIT. P. MANTEUFEL and E. KOTTMANN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **74**:25, 1932.

The technic of E. Löwenstein was exactly followed, though his latest modification was not yet available. A growth was obtained from postmortem blood specimens of all five rabbits examined. Of thirty-four cultures taken intra vitam, only four gave growth. Thus far there can be no important diagnostic significance attached to the blood culture for the diagnosis of experimental tuberculosis in the rabbit.

I. DAVIDSOHN.

ACID-FAST BACILLI. FRANZ EICHBAUM, Ztschr. f. Immunitätsforsch. u. exper. Therap. **74**:31, 1932.

I. Pure cultures of acid-fast water bacteria were grown from spigots and from the attached rubber tubing in over 50 per cent of the examinations. They

were also found in running water. Acid-fastness was occasionally only relative. They were nonpathogenic for guinea-pigs. The ability of these bacteria to grow in the presence of metals, particularly silver and copper, which are harmful to other bacteria, and their optimum temperature (22 C.) are means of differentiation from tubercle bacilli, for which they can be easily mistaken in stained preparations. II. A check of Shiga's technic for the cultivation of bacilli of leprosy was made with similar results: a definite growth was obtained only in two generations, with a possible growth also in the third. III. A check of the results of Löwenstein in blood cultures for tubercle bacilli was made on a small number of cases (twenty), following the older technic. The results were negative. IV. The technic used for guinea-pig inoculation for the diagnosis of tuberculosis at the Hygienic Institute of the University in Frankfurt-on-the-Main is described. Only one possible case of spontaneous tuberculous infection in a guinea-pig over a period of decades was observed.

I. DAVIDSOHN.

C-FORM OF THE TUBERCLE BACILLUS. PHILALETHES KUHN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **74**:93, 1932.

The tubercle bacillus occurs also in a coccoid, nonacid-fast, granular, so-called C-form, identical with some of the gram-positive granules described by Much. The granular form can be obtained from liquid cultures of tubercle bacilli by treatment with ammonia and heating. The C-forms grow on proper mediums; their colonies contain some rods which vary with regard to acid-fastness. Their filtrability is assumed, though not established. The existence of a filtrable virus stage of the tubercle bacillus is not established.

I. DAVIDSOHN.

VARIABILITY OF BOVINE TUBERCLE BACILLI. WALTER SEIFFERT, Ztschr. f. Immunitätsforsch. u. exper. Therap. **74**:116, 1932.

Three virulent strains and one avirulent strain were studied. The avirulent strain was grown from B C G vaccine; one of the virulent strains was obtained by dissociation from a B C G culture. A morphologic change was noticed in the stained preparations, consisting in a formation of granules in the bacilli, associated with a simultaneous degenerative change in the protoplasm. The change is looked on as similar to the phenomenon of d'Herelle. Variable colony formation and morphologic and tinctorial changes were observed. The changes were distinctly related to the composition of the culture mediums. There were also connections between the morphologic structure of the bacteria and the type of colony.

I. DAVIDSOHN.

Tumors

RETROPERITONEAL TERATOMA. C. FROBOESE, Frankfurt. Ztschr. f. Path. **43**:222, 1932.

The tumor was found at autopsy in a girl 1½ years of age. The reason for the publication of the report was the presence of anterior hypophyseal hormone in the urine. The author quotes Zondek as having stated that this is the first demonstration of this hormone in a patient with a benign tumor.

O. SAPHIR.

TUMORS OF THE NASAL CAVITY. K. H. MICHEL, Frankfurt. Ztschr. f. Path. **43**:354, 1932.

The tumors of the nasal cavity and of the ethmoid bone and also those arising in the region of the palate, upper lip and orbits, as a rule, described as endotheliomas or cylindromas, are closely related to organoid tumors arising from the salivary glands. Histogenically, according to Mathias, they should be termed progonomas, because they might arise from misplaced tissue as the result of fetal atavism. All tumors of the maxilla which are suggestive of carcinoma should be

examined carefully so as to rule out a possible origin in the parotid gland. This is of clinical importance because of the relatively lower malignancy of tumors arising in the parotid gland.

O. SAPHIR.

SARCOMA OF THE EYE. L. HEINE, Virchows Arch. f. path. Anat. **280**:122, 1931.

The origin of a melanoma of the eye is ascribed to a pigmented ciliary muscle. The tumor was unusual in its mode of spread through the sclera and in the polymorphism of its cells. The spread of the tumor within the sclera is held to have been due to the ameboid activity of the tumor cells. Nine examples of small sarcomas of the sclera are described. These were discovered in eyes removed for some reason other than tumor.

O. T. SCHULTZ.

TWO CHROMAFFIN TUMORS OF THE SYMPATHETIC SYSTEM. M. NORDMANN and E. LEBKÜCHNER, Virchows Arch. f. path. Anat. **280**:153, 1932.

Tumors derived from the elements of the sympathetic nervous system origin, often termed paragangliomas, arise not infrequently from the medulla of the suprarenal. Some of these tumors are composed of chromaffin cells and have been named pheochromocytomas. Chromaffin tumors arising from sympathetic ganglia or from the sympathetic trunk are rare. The authors tabulate three previously reported cases and add two. Of the previously reported cases, two arose from paraganglionic tissue and were situated at the bifurcation of the aorta, and one arose from the sympathetic trunk. In one of the authors' cases, the tumor was situated at the aortic bifurcation. It was the size of a kidney, was encapsulated and was grossly and histologically benign. The tissue had a brown color. The other tumor was the size of a man's fist, arose from the sympathetic trunk and was situated behind the pleura in the region of the costovertebral junction of the seventh and eighth ribs. The growth was infiltrative, and the tissue was brown. The fresh tissue of each tumor gave the physiologic reactions of epinephrine. The fixed tissue and the brown stained fixing fluids yielded a positive Vulpian's reaction for quaiacolbenzyl ester (*Brenzkatechin*). The fixed tissues gave only weak chromaffin and other reactions of epinephrine. The benign tumor situated at the bifurcation of the aorta, a pheochromocytoma, was a chance observation in a medicolegal necropsy; the clinical history was not known, but there was no arteriosclerosis or other anatomic evidence of an increased output of epinephrine by the tumor. The malignant tumor, a pheochromocytoblastoma, occurred in a woman aged 35 years. The systolic blood pressure of 200 mm. and the clinical symptoms of palpitation, dyspnea, hyperhidrosis, tremor, constipation, loss of hair and loss of strength and weight are ascribed to an increased output of epinephrine by the neoplasm.

O. T. SCHULTZ.

HISTOGENESIS OF MIXED TUMORS OF THE SALIVARY GLANDS. E. KUX, Virchows Arch. f. path. Anat. **280**:175, 1931.

The origin of mixed tumors of the salivary glands is still a matter of controversy. The author's attempts to determine whether such tumors are of mesenchymal epithelial or combined mesenchymal and epithelial origin were based on the histologic and microchemical study of eight tumors, only four of which, however, were suitable for complete study. Especial attention was paid to the concentrically laminated bodies found in such tumors and to the cartilage-like areas. If the latter are composed of true cartilage, the mixed character of the tumors is established. The concentric bodies may be of either epithelial or endothelial origin. In the former case they are derived from epithelium of squamous character or from the epithelium of glands the secretion of which cannot escape. The endothelial bodies are derived from small blood vessels. The cartilage-like areas are composed of true cartilage. The author concludes that the tumors contain derivatives of two germ layers and are true mixed tumors.

O. T. SCHULTZ.

A Case of Diffuse Meningeal Carcinomatosis. Helene Schuster, Virchows Arch. f. path. Anat. **280**:194, 1931.

The condition described occurred in a woman aged 57 years. The pia-arachnoid was diffusely thickened, but its gross appearance did not suggest neoplasm. Microscopically, it was found to be diffusely invaded by tubular and acinar structures composed of columnar epithelium. The origin of the tumor was the surface epithelium of the choroid plexus of the third ventricle.

O. T. Schultz.

Rhabdomyoblastoma. A. I. Abrikossoff, Virchows Arch. f. path. Anat. **280**:723, 1931; W. Ceelen, ibid. **280**:741, 1931.

For tumors composed of large, round or oval cells with the morphology of embryonic myoblasts, of which he had previously described five, Abrikossoff proposed the name myoblastmyoma. He describes five additional similar tumors and discusses their origin. The tumors were small and occurred either where striped muscle is normally found, as in the tongue or voluntary musculature, or in situations where striped muscle does not normally occur, such as the skin, vocal cord, esophagus and breast. He describes also two small nodular tumors of the alveolar process of the lower jaw. These were composed of larger cells with multiple nuclei, cells that the author terms hypertrophied myoblasts. When the tumors arise in a situation where striped muscle does not normally occur they are the result of embryonic maldevelopment. Tumors of the kind under discussion Abrikossoff divides into four groups: typical myoblastmyoma, composed of myoblasts of embryonic type; differentiating myoblastmyoma, in which some of the myoblasts are differentiated into elongated cells with longitudinal and transverse striations; hypertrophic myoblastmyoma, made up of enlarged myoblasts with multiple nuclei; malignant myoblastmyoma or myoblastsarcoma. Ceelen gives a description of four small tumors that belong in Abrikossoff's group of typical myoblastmyomas. In two adults the growths were situated in the tongue and the skin, respectively. Two occurred beneath the mucosa of the lower and upper jaws of new-born infants. The latter observations establish the dysontogenetic origin of such tumors.

O. T. Schultz.

The Relationship Between Embryonal and Carcinomatous Tissue. L. Hirszfeld and W. Halber, Ztschr. f. Immunitätsforsch. u. exper. Therap. **75**:193, 1932.

Some serums obtained by immunizing rabbits with rat embryos fixed complement only with alcoholic extracts of rat placenta and rat sarcoma, and of human cancerous tissue, but not with other rat or with human organs. Immune serums, produced by injecting rabbits with normal organs and with the placenta of adult rats and of rat sarcoma, fixed complement with cancerous tissue from human beings stronger than with normal human organs. According to Hirszfeld and Halber, there is no compelling need for assuming an antigenic similarity between rat embryos and human cancer. The described reactions may be explained by the factors of increased serologic reactivity of the lipoids in the cancerous tissue and of the disturbed colloid balance of the serum of rabbits injected with embryonal tissue. In the second part, on "Human Embryo and Cancer" the author states that some rabbit immune serums produced with human cancerous tissues fixed complement with extracts of human embryonal tissue but not with extracts of adult organs. Results of cross-absorption of the immune serum with extracts of cancerous and of embryonal tissues pointed also in the direction of some antigenic relationship. Blood serums of pregnant women, which react in the complement-fixation test with extracts of cancerous tissue, did not react with extracts of embryonal tissue.

I. Davidsohn.

THE SO-CALLED ERYTHROLEUKOSIS IN CHICKENS. J. ENGELBRETH-HOLM, Ztschr. f. Immunitätsforsch. u. exper. Therap. **75**:425, 1932.

The term "chickenleukosis" was suggested by Ellermann and Bang, in 1908, for a group of diseases which are similar to, though not identical with, leukemia in man. Engelbreth-Holm presents in this report the results of a study of successful transmission of erythroleukosis through ten generations of chickens, with 110 "takes" among 183 inoculated animals. In the first passage in only two cases was the process one of a mixed myeloid-erythroleukotic nature; the remainder were pure cases of erythroleukosis. The failure of noting even a single case of lymphatic leukosis confirms the contention of J. Furth that lymphatic leukosis is a disease *sui generis*. With the increasing number of passages, an increase of the percentages of "takes" (from 15 per cent up to 100 per cent) and a shortening of the period of incubation (from three hundred days to one week) were noted. Inoculations were successful by the intravenous, intramuscular and subcutaneous routes, but not by the oral route. A detailed anatomic, histologic and hematologic analysis is included, with fifteen photomicrographs. The characteristic blood cells are the so-called "erythrogonia," which are probably progenitors of the mature red blood cells. They are normally found only in the bone marrow, but during the disease they are present in large numbers (as great as 650,000 per cubic millimeter) in the circulation. A moderate to marked anemia and some leukopenia are present. There are no evidences of inflammation, no leukocytosis, no necrosis or evidences of degeneration and no rise in temperature. In a few cases, tumorlike formations, consisting of masses of erythrogonia, were found in the viscera, in the skin and in the musculature. The nuclei of the erythrogonia are larger than the nuclei of normal erythrogonia in the bone marrow of normal animals. The disease is strictly species-specific and could not be transmitted even to closely related species. Engelbreth-Holm favors the conception of the neoplastic nature of the disease in chicken, as opposed to the infectious hypothesis.

I. DAVIDSOHN.

ALTERED BEHAVIOR OF RED CELLS OF CANCEROUS SUBJECTS AFTER EXPOSURE TO FLUORESCING SUBSTANCES. A. H. ROFFO, Ztschr. f. Krebsforsch. **35**:130, 1932.

Since the lytic effect of fluorescing substances on erythrocytes is as a rule manifest only after their exposure to light, this has been explained as resulting from their oxidation after sensitization to light by the dye. Starting with the theory that the oxidation-reduction balance should be altered in the blood of cancerous subjects, Roffo tested the behavior of their erythrocytes in relation to the aforementioned phenomenon, and found that with some fluorescing dyes, particularly erythrosin, excessive hemolysis occurred in the circumstances. He suggests that this alteration may be of diagnostic value.

H. E. EGGERS.

COINCIDENT CARCINOMA AND TUBERCULOSIS OF THE TESTIS. W. PFLUGRADT, Ztschr. f. Krebsforsch. **35**:164, 1932.

Pflugradt reports two cases of associated tuberculosis and carcinoma of the testis. In the first, there were scattered tubercles present both in the tumor and the testicular stroma, and the infection was in sequence to tuberculosis of the epididymis. In the second case the tuberculosis occurred as a diffuse involvement of the interstitial tissues. There was no tuberculous epididymitis in this case, and in view of the extreme rarity of primary tuberculosis of the testis, the author believes that its occurrence is due to the lowering of local resistance incident to the primary involvement by cancer.

H. E. EGGERS.

SEROLOGIC REACTIONS IN MALIGNANT DISEASE. H. SACHS, Ztschr. f. Krebsforsch. **35**:275, 1932.

In connection with a description of an attempt at the serologic diagnosis of cancer, in which Sachs used a method of precipitation of lecithin suspension by

the serum of the patient, he discusses the general possibility of the development of reliable serologic reactions for cancer. His own test cannot be regarded as definitely diagnostic, as in 225 known cancerous cases he obtained 52.8 per cent of positive and 8 per cent of doubtful reactions, although in noncancerous controls the corresponding figures were 7.4 per cent and 1.9 per cent. Since the greater proportion of false positive tests occurred in association with diseases of great constitutional gravity, such as tuberculosis, sepsis and echinococcus infection, the test cannot be regarded as having any great differential value. Sachs points out that the mere presence of bodies of antigenic character in a person would not necessarily imply the production of specific antibodies, since it is a recognized principle that antibodies are not produced to self-generated antigens. With a properly refined technic, alterations of lability, such as are indicated by the test he describes, while nonspecific, may differ sufficiently to serve as diagnostic criteria.

H. E. Eggers.

Carcinoma of the Vocal Cords. F. Blumenfeld, Ztschr. f. Krebsforsch. **35**:360, 1932.

In a general discussion of the subject, Blumenfeld points out their greatly disproportionate incidence in males; the fact that they rarely cause lymphatic metastasis, and then usually in connection with involvement of the anterior portions of Poirier's glands and the absence of peculiarities as to age incidence. A peculiarity which he emphasizes is the existence of an early stage in which local removal is sufficient for permanent cure; this is true as long as infiltration is limited to the elastic tissues of the cord, while after infiltration into the muscular tissues, which is indicated by fixation of the cord or great restriction of its motility, this stage has been passed, and more radical operation is called for.

H. E. Eggers.

The Primary Malignant Tumors of the Serous Cavities. R. Grossek, Ztschr. f. Krebsforsch. **35**:435, 1932.

In a discussion of the possibilities of origin of malignant tumors of the serous cavities, Grossek recognizes three: origin from embryologically displaced epithelium, from lymphatic endothelium and from the lining cells of the cavity. Those coming from lymphatic endothelium may be legitimately termed endotheliomas, but with the tumors originating in the lining membranes, uncertainty as to the exact character of these leads to a corresponding uncertainty of classification of the neoplasms. Grossek believes that these tumors should not be classified by tissue of origin, but by clinical and morphologic characteristics. The fact that these tumors partake so usually of the characteristics of true carcinoma would appear to be evidence in favor of the epithelial character of these lining membranes.

H. E. Eggers.

Tracheal Involvement in Generalized Lymphosarcomatosis. M. Plonskier, Ztschr. f. Krebsforsch. **35**:467, 1932.

A case of generalized lymphosarcomatosis with multiple and peculiar tracheal involvement in the form of polypoid lymphoid tumors of the mucosa and submucosa is reported in considerable detail. As concerns the origin of these, Plonskier believes that they are not to be regarded as metastatic tumors. Involvement by continuous growth would appear to be excluded as a possibility largely because of the actual separation of the lesions from those of the nearest lymphadenoid tissue. Transmission by way of the lymphatics was improbable, as invaded lymphatics occurred in intact portions of the trachea and frequently not near the tracheal tumors. The same reasons apply to transmission along the perivascular clefts. But Plonskier's principal reason for regarding the lesions as autochthonous is the presence in them of a well developed reticulum, which was conspicuously

absent in all lesions of a definitely secondary character. He regards the tracheal tumors as an expression of the generally enhanced lymphadenoid proliferation which appears to be typical of this type of tumor.

H. E. EGGERS.

"DISSEMINATED CARCINOMA" OF THE STOMACH. R. ERNST, Ztschr. f. Krebsforsch. **35**:585, 1932.

In a discussion of "disseminated carcinoma" of the stomach, the term being used in the sense introduced by Krompecher to indicate cancer with extreme epithelial metaplasia and with diffuse infiltration in the form of scattered small nests of cells, and even single cells, Ernst speculates as to the probable cause of this type of growth. He suggests that it may possibly be due to persistent secretion of hydrochloric acid by the tumor cells, by which they induce an acidity of their milieu unfavorable to themselves and a stimulant to the overgrowth of connective tissue. Ernst admits that his explanation is purely hypothetical.

H. E. EGGERS.

THE BENDIEN FLOCCULATION TEST IN MALIGNANT CONDITIONS. E. MEYER, Ztschr. f. Krebsforsch. **35**:622, 1932.

Last year Bendien published an account of a test which he believed to be of diagnostic value in cancer, based on the varying flocculation of the serum by a vanadium-acetic acid mixture. In a study of this reaction in a variety of diseases, Meyer reaches the conclusion that the test is of no value. He obtained positive results in the absence of cancer and negative ones in that disease, in proportions that would suggest that the test is without even presumptive value.

H. E. EGGERS.

METASTASIS OF PRIMARY CANCER OF THE LUNG. E. ASK-UPMARK, Acta path. et microbiol. Scandinav. **9**:239, 1932.

Primary cancer of the lung distributes its metastases directly by the general arterial circulation. In 2,080 cases of such a tumor, metastatic growths were most frequent in the liver; next in frequency were the bones, the kidneys the suprarenals, the central nervous system, the pancreas, the thyroid, the gastrointestinal tract, the heart, the spleen, the skin, the ovaries and the muscles.

FROM THE AUTHOR'S SUMMARY.

Medicolegal Pathology

ABSORPTION AND DISTRIBUTION OF ARSENIC IN THE HUMAN BODY FOLLOWING ITS EXTERNAL APPLICATION. L. FUCHS, Deutsche Ztschr. f. d. ges. gerichtl. Med. **19**:280, 1932.

The internal organs in four lethal cases of inoperable external carcinoma, in which the patients were treated with arsenic salves, were examined for arsenic. Most of the arsenic was excreted through the kidneys during life, more than was detected in all of the analyzed internal organs together. Eighteen days after the treatment was discontinued, it was found that the lungs were entirely negative for arsenic; therefore, this organ cannot be considered as an arsenic depot. In one case the brain contained three times as much arsenic as the liver; in the other cases, the latter organ and the kidneys showed an accumulation of nearly equal quantities. However, in the bones, arsenic was deposited in large amounts, which is of great forensic importance.

E. L. MILOSLAVICH.

IDENTIFICATION OF SKELETAL REMAINS. E. GIESE, Deutsche Ztschr. f. d. ges. gerichtl. Med. **19**:285, 1932.

So that his wife might collect a large sum of life insurance money, a husband feigned that his death was being planned. A few months later, a completely decayed body, with the face thoroughly crushed, was discovered in a forest. Several objects, such as a monogrammed watch and ring, a pocket knife and keys, were found on the body and identified as those belonging to the husband. Examination of the teeth, but particularly of the skeleton, proved beyond any doubt that the body found was not that of the man in question. The morphologic examination of the bones is presented in minute details. Both feet were missing, since they had been severed with a hatchet and destroyed, apparently to mislead one in determining the height of the body or because they may have shown some peculiar marks, such as hallus valgus, hammer toe, etc., which are important for proper identification.

E. L. MILOSLAVICH.

CHANGES IN THE MUCOUS MEMBRANE OF THE UPPER RESPIRATORY TRACT IN DEATH BY BURNING. A. FOERSTER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **19**:293, 1932.

When a burnt body is found, the first question that arises is whether the burning occurred during life or after death. The aspiration of soot in the deeper air passages, the presence of carbon monoxide in the blood and changes in the upper respiratory tract due to the action of heat are of diagnostic value. The inhalation of hot air produces a necrosis of the mucous lining of the larynx and trachea, which becomes detached in shreds or membranes. The epithelial cells are transformed into rodlike or star-shaped structures, similar to the changes of the skin caused by sudden intense heat.

E. L. MILOSLAVICH.

ELECTRIC ACCIDENTS IN MINING. F. PIETRUSKY and G. SCHRADER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **19**:313, 1932.

The authors present a statistical analysis of 589 cases, 121 of which ended lethally; 72 patients sustained severe permanent injuries. Electrical currents up to 220 volts caused the death of 21 persons. In several instances, other severe injuries, such as fracture of the skull or internal traumatisms due to a fall at the time of contact with the electrical current, followed concomitantly. The ratio of the voltage to the number of fatal cases and the severe and minor electrical injuries was as follows: for currents up to 220 volts, 21:5:52; for currents up to 500 volts, 26:11:54, and for high tension currents, 67:37:73. In several instances late hemorrhages and necrosis of large areas of tissues developed on account of the extensive alterations in the blood vessels.

E. L. MILOSLAVICH.

Book Reviews

Der Coronarkreislauf, Physiologie, Pathologie, Therapie. By Dr. Max Hochrein, Professor an der Universität Leipzig. Price, 24 marks. Pp. 227, with 54 illustrations. Berlin: Julius Springer, 1932.

After a short résumé of the anatomy of the coronary system the author considers at length the experimental work that has been done on the coronary arteries. These pages, 16 to 90, are the most important in the work, for they embrace real and relatively recent contributions to the knowledge of the subject. The methods of investigation are outlined; the work of others is subjected to critical analysis; the researches of the author and his associates are discussed with special fulness, and conclusions are frankly and clearly stated. The summaries at the end of each topic are extremely helpful. As examples of the subjects taken up may be mentioned pressure in the coronary arteries, examination of isolated coronary arteries, the mechanism of the coronary circulation, the autonomic regulation of the blood stream in the coronary artery, the coronary circulation and respiration and the pharmacology of the coronary vessels. It may be mentioned in passing that Hochrein several times reaches conclusions that are different from those of Anrep, whose views have had wide acceptance.

The last part of the work, about a hundred pages, is given over to diseases of the coronary system. A brief outline of the anatomy, pathology and physiology of coronary disease is followed by the more extended portrayal of clinical features. These are discussed under heads of general symptomatology; symptom complexes, which include angina pectoris, cardiac asthma, and paroxysmal tachycardia; special coronary disease, including sclerosis, syphilis and coronary thrombosis, and treatment.

When we say that there is little in these chapters on clinical features that is new to American students of cardiology, there is no intent to imply a condemnation of what Hochrein has written regarding the clinical aspects of coronary disease. It merely means that American physicians have for several years been conversant with practically all the features here portrayed. One feels that this portion of the subject is not as clearly and as systematically handled as the experimental part. Often, as in the consideration of the electrocardiogram, there seems to be a vagueness in the statements almost giving an impression of uncertainty on the part of the writer. This uncertainty seems strikingly emphasized when by way of contrast we read his brief chapter on myodegeneration of the heart. Here the author, dealing with older, more familiar facts and methods of diagnosis, has presented the subject in a remarkably compact form that is clear, orderly, convincing. It is a model chapter, one of the best brief ones on this topic we have ever read.

Hochrein speaks of angina pectoris as a symptom complex and divides it into three classes: a vasomotor angina pectoris, true angina pectoris on an organic (coronary) basis and myocardial infarct (coronary thrombosis). The vasomotor type is stressed more than it commonly is in the United States. While classified under the head of the symptom complex of angina pectoris, myocardial infarct is described several pages further on under the head of special diseases of the coronary system. The symptoms of what is commonly called angina of effort, and of coronary thrombosis, are well set forth, though, as already stated, there seems to be a little confusion as to differentiation as there is as to classification. The embolic phenomena of coronary thrombosis that are due to the formation of intracardiac thrombi seem to be overlooked. The atypical and milder forms of thrombosis might be more fully considered, as might the frequency of recurrences. The fact that the electrocardiogram after coronary thrombosis changes in character from day to day is not sufficiently emphasized.

One must approve the conservatism of the author. He often refers to the fact that we may not speak too positively on certain points because our knowledge is yet far from complete. His words of caution regarding the interpretation of electrocardiograms, x-ray films, the clinical symptoms and even the facts as to the anatomy of the coronary arteries are timely. The author is also well aware that clinical and experimental observations should be mutually helpful and mutually critical. In one place he says: "and so clinical observations came out ahead"; that is, they disproved the conclusions arrived at by experiment. This attitude of healthy skepticism helps us to have confidence in his statements of fact as well as of opinion. It is with something of surprise, therefore, that we note in his chapter on treatment the apparently abounding faith he has in drugs in the treatment of coronary disease. Long lists of proprietary medicines, use of which is advised, remind us of the advertising pages of German medical weeklies. They make us feel that he is decidedly a therapeutic optimist.

His references in the text show an intimate familiarity with the literature on the subject. His bibliography, while not pretending to be complete, is extensive. We have, in glancing through his list of names, felt that there are here and there strange omissions. The work of F. N. Wilson has not received the attention it deserves. The South American writers, Battro, Padilla and Cossio, are worthy of notice.

Altogether the book is a real contribution and gives proof, if proof were needed, that the German clinicians, even though a little late, are wide awake to the importance of disease of the coronary artery.

***p*H and Its Practical Application.** By Frank L. La Motte, William R. Kenny and Allen B. Reed. Price, $3.50. Pp. 262, with 18 charts and 15 figures. Baltimore: Williams & Wilkins Company, 1932.

The quantity of acid or alkali in any chemical system has since early days in chemistry been determined by titration. Even the first chemists knew that this value did not measure the intensity of their action, but no understanding of this factor was given until the physical chemists (particularly Svante Arrhenius) in the late eighties of the last century brought forward the concept of electrolytic dissociation and declared the "strength" of acids and alkalis to depend, not on their molar concentration, but on the concentration of the hydrogen or hydroxyl ions yielded on dissociation. They devised at the same time an electrical method for the measurement of such concentration. Shortly thereafter the "indicators" (like litmus, turmeric, rosolic acid or phenolphthalein) used by the older chemists to "indicate" by change in color when their systems were acid, alkaline or neutral were checked against such electrical determinations of hydrogen or hydroxyl ion concentration, and a colorimetric method of measurement was at hand. With the spectroscopic method developed by Wallace R. Brode (1924) we possess today three methods for the determination of this physiochemical variant.

This book by La Motte, Kenny and Reed deals chiefly with the second of these methods for determining hydrogen ion concentration. Since the days when only colored vegetable extracts were available to the chemist as indicators, unnumbered scores of synthetic dyes have been placed at his disposal. To make them of use in hydrogen ion determination they had to be sorted, only such being retained as were chemically stabile under conditions of work, more or less "sharp" as to end-point and stabile as to color change in the solutions into which they were dropped except with variation in their hydrogen or hydroxyl ion concentration. The senior author of this volume, with William Mansfield Clark and Herbert A. Lubs, is chiefly responsible in this country for such selection which puts the stamp of authority on the methods discussed in this volume.

In the first fourth of the book the authors give a fair outline of what is meant by electrolytic dissociation, buffer action and concentration of hydrogen ions. In place of the older designation of the last-named value, namely C_H, there is chosen S. P. L., Sørensen's p_H. (For some atrocious reason Sørensen's name is spelled Sorensen throughout.) The last three-fourths have to do with the practical business

of utilizing standardized indicators for measuring the hydrogen ion concentration in every conceivable type of system from water supplies through sewage to soda crackers. The authors are happily modest in the claims made for the reliability of their methods as applied to all such systems and yet more modest in their interpretation of the actual measurements, leaving this, for the most part, to the authors of the many papers quoted which, on review, turn out to be almost exclusively American. La Motte, Kenny and Reed rightly emphasize the "errors" incident to their colorimetric determinations. It would be well if the readers and the appliers of their technic would bear them in mind. These colorimetric determinations of hydrogen ions are applicable without modification only to dilute and to aqueous solutions and to such only when (presumably) "homogeneous" or "monophasic." But this is not the type of "solution" that characterizes that great cosmos which is represented by physiology, pathology, lyophilic colloid chemistry, leather, textiles, paper, cereals, soaps or soils.

Endocrine Medicine. By [the Late] William Engelbach, M.D., F.A.C.P., B.S., M.S., D.Sc., Professor of Clinical Medicine, St. Louis University School of Medicine, 1911-1924. With a Foreword by Lewellys F. Barker, Professor Emeritus of Medicine, Johns Hopkins University. Three volumes and an index volume with 933 illustrations. Price, $35. Volume I. General Considerations, pp. 460. Volume II. The Infantile and the Juvenile Endocrinopathies, pp. 473. Volume III. The Adolescent and the Adult Endocrinopathies, pp. 862. Volume IV. Bibliography, Index of Names, Index of Subjects, pp. 117. Springfield, Ill.: Charles C. Thomas, 1933.

The first volume of Engelbach's treatise is entitled "General Consideration" and deals with the history of endocrinology, general comments on the structure and the functions of the endocrine organs, the endogenous and exogenous factors concerned in the etiology of the endocrinopathies, the general diagnostic procedure, the special study of basal metabolism, of hormonic and specific reactions and of the chemical composition of the blood and the relations of endocrinology to general medicine, to the medical and surgical specialties and to public health.

The second volume is devoted entirely to the "Infantile and Juvenile Endocrinopathies." In it special attention is paid to disorders of the thyroid, the hypophysis, the gonads, the parathyroids and the thymus.

The third volume describes the endocrinopathies of adolescents and adults. Though here all the organs of the endocrine system are given consideration, the thyroid and the pituitary gland, as might have been expected from the author's previous publications, receive his major attention.

The pathologic anatomy and the pathologic histology of the hormone-producing organs are described and illustrated, but it is the pathologic physiology of hypofunction, hyperfunction and dysfunction, as well as the reciprocal relations among the different organs of internal secretion when they are diseased, on which most stress is laid.

It should be helpful to pathologists to have the opinions of this endocrinologist of large experience to supplement the observations of the contributors to "Endocrinology and Metabolism" (Appleton), of von Gierke (in Aschoff's textbook), of Biedl, of Gley, of Schäfer, of Swale Vincent, of Falta and of the contributors to the large handbook edited by Hirsch.

Final Report of the Commission on Medical Education. Price, $2. Pp. 560. New York: Columbia University Press, 1932.

No attempt will be made to offer a critical and detailed analysis of this report, which embodies the well considered conclusions of a comprehensive and thorough study of medical education in this country, with particular emphasis on the present needs of the public for medical service. Medical knowledge is in advance of its application. The circumstances of the formation of the Commission on Medical

Education and the evolution of medical education in the United States are discussed briefly in the foreword and introduction. An enumeration of the chapter headings will indicate the general scope of the report: the public aspects of medicine, medical needs, the supply and distribution of physicians, postgraduate medical education, the internship, medical licensure, the medical cause, opinions regarding medical training, premedical education, the cost of medical education, medical education in Europe (Great Britain, Germany, France, Austria, Switzerland, The Netherlands, Denmark and Sweden) and a summary, which is a comprehensive epitome of the report. The appendix contains a large amount of tabular material gathered by the Commission in the course of its work. "The study and report deal with the education of medical students, and attention is focused upon that problem particularly. Reference is made only incidentally to problems of research, clinical facilities, administration, staff organization, and finance. The importance of these features as they influence the program of training, the selection of the teaching staff, the advancement of knowledge, and the quality of medical instruction, and the extent to which they differ among universities are fully appreciated" (foreword). The report will meet with general approval. It is a constructive and stimulating contribution. Clear vision, a broad grasp and sound judgment prevail. It will be a noteworthy landmark in the history of medical education in this country. It will be studied with keen interest by all who are concerned actively in guiding and influencing the education of medical students and physicians. Teachers of nonclinical branches should study the report with particular reference to adjusting the opportunities their departments offer the student to learn to the best advantage of the medical curriculum as a whole.

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